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Review

Treatment

Role of agmatine in cognitive functions

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Abstract

Introduction

Agmatine, an endogenous amine, is synthesised through decarboxylation of L-arginine by mitochondrial enzyme arginine decarboxylase and metabolised either by agmatinase into different polyamines such as putrescine, spermine and spermidine, or by diamine oxidase to guanido butanoic acid and it has been known to be widely distributed throughout the body.

Agmatine has been suggested as a novel neurotransmitter and/or neuromodulator in mammalian brain, as it is synthesised in the brain and also in the spinal cord, stored in and released from synaptic vesicles in region-specific neurons by Ca^{2+}-dependent depolarisation, inactivated by reuptake and metabolised by agmatinase, a specific enzyme for agmatine. Because the concentration of agmatine in the brain is comparable to that of classic neurotransmitters, it has been considered as a putative neurotransmitter.

Agmatine exhibits its biological effects in the central nervous system by interacting with certain receptors and neuronal pathways. It binds to imidazoline-binding sites and α_2-adrenoreceptors and blocks N-methyl-D-aspartate receptors via voltage- and concentration-dependent mechanisms and other ligand-gated cationic channels including nicotinic and 5-HT_3 receptors. Additionally, it is a competitive inhibitor of both neuronal nitric oxide synthase and inducible nitric oxide synthase but it conversely stimulates endothelial nitric oxide synthase. Agmatine has been shown to prevent all naloxone-precipitated withdrawal signs in morphine dependence and to provide analgesic, anti-inflammatory, anticonvulsant, neuroprotective, anxiolytic and antidepressant activities. However, its role in cognition has not been extensively investigated. Now, there is accumulating evidence of that agmatine having noticeable effects on learning and memory in experimental animal models. The main purpose of this review is to discuss the biological role/therapeutic potential of agmatine on cognitive functions/deficits based on published research studies.

Conclusion

Agmatine might be accepted as a future therapy for cognitive disorders; however, the exact mechanism of agmatine's effect on learning and memory remains unclear at present. Further studies should be addressed to understand the underlying mechanism of both physiological and pharmacological agmatine's effects in learning and memory.

Introduction

Although a German scientist, Albrecht Kossel, first discovered agmatine in 1910, its biological and physiological effects remained unexplained until late 20th century. Agmatine (4-[aminobutyl] guanidine), an endogenous polycationic amine, had long been known to be present in bacteria, plants and invertebrates[1]. It was isolated from rats brain as a result of a searching an endogenous ligand for imidazoline-binding sites and led to the discovery of its expression in the mammalian brain[2].

Agmatine is synthesised through decarboxylation of L-arginine (a semi-essential amino acid) by the mitochondrial enzyme arginine decarboxylase (ADC) and metabolised either by agmatinase into different polyamines such as putrescine, spermine and spermidine, or by diamine oxidase to guanidobutanoic acid[3,4] (Figure 1).

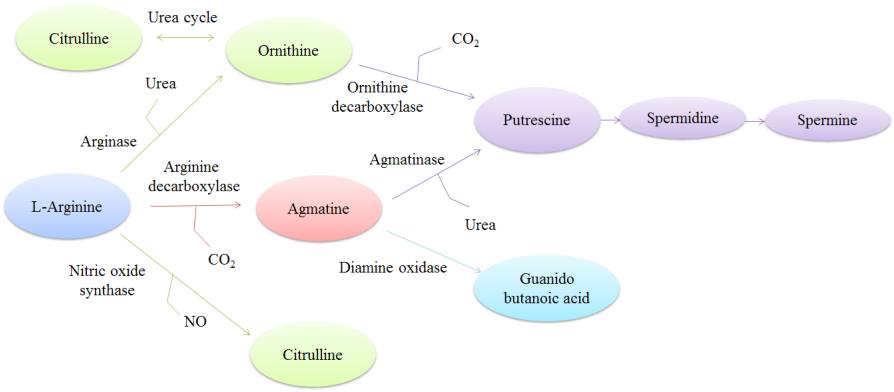

Figure 1: Three distinct metabolic pathways of L-arginine among which agmatine is synthased from L-arginine by arginine decarboxylase and metabolised to both putrescine, forming spermidine and spermine by agmatinase and to guanidobutanoic acid by diamine oxidase enzymes.

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Besides its relatively low concentration in the brain, agmatine has been known to be widely distributed throughout the body. It has been detected in many organs; mostly in the stomach, aorta, small intestine, adrenal gland, heart, brain, colon and plasma (see Table 1). Likewise, ADC and agmatinase have also been found in many other organs such as the stomach, small intestine and aorta[5–8].

Although it is detected as an endogenous substance, agmatine is also found in food products, led by fermented food and marine fishery[9]. Because of the low arginine–ADC activity in mammalians, the amounts of agmatine found in tissues may be minimally ascribed to an endogenous *de novo* synthesis by the enzyme, while a great quantity of agmatine may be of dietary origin[9].

Agmatine, an aliphatic polar cationic amine with low molecular weight, has been suggested as a novel neurotransmitter and/or neuromodulator in the mammalian brain[5,8,10] for several compelling reasons including that it is synthesised in the brain and also in the spinal cord, stored in and released from synaptic vesicles in region-specific neurons by Ca^{2+}-dependent depolarisation, inactivated by reuptake and metabolised by agmatinase, a specific enzyme for agmatine. Furthermore, because the concentration of agmatine in the brain is comparable to that of classic neurotransmitters supports the idea that it might be considered as a putative neurotransmitter[8].

Agmatine exhibits its biological effects in the central nervous system (CNS) by interacting with certain receptors and neuronal pathways. It has been shown by several previous studies that agmatine binds to imidazoline-binding sites[11] and α_2-adrenoreceptors and blocks N-methyl-D-aspartate (NMDA) receptors via voltage- and concentration-dependent mechanisms and other ligand-gated cationic channels including nicotinic and 5-HT_3 receptors[7,8,11–13].

In earlier studies, agmatine has been shown to be a competitive inhibitor of both neuronal nitric oxide synthase (nNOS) and inducible NOS (iNOS)[14] or to inhibit all three isoforms of NOS including endothelial NOS (eNOS)[15]. However, it was recently found that it conversely stimulates eNOS in the rat brain after cerebral ischaemia[16].

In the brain, agmatine has been shown to demonstrate rather regional and heterogeneous distribution. When Otake et al.[17] immunohistochemically mapped the distribution of agmatine in a rat brain and determined agmatine-like immunoreactivity via using a specific polyclonal anti-agmatine antibody, they found that agmatine was mostly expressed in the rostral brainstem and forebrain. The findings of their study showed that the hypothalamus, rostral midbrain, periventricular areas including the laterodorsal nucleus, locus coeruleus, nucleus raphe dorsalis and periaqueductal grey were the primary regions wherein agmatine-like immunoreactivity was mostly expressed[17].

Soon afterwards another study, examining the cellular and subcellular localisation of agmatine in the hippocampus, revealed that in the hippocampus agmatine was found primarily in the axon terminals of pyramidal cells forming excitatory or asymmetric synapses. It was suggested that agmatine may be co-stored with L-glutamate since hippocampal pyramidal cells mainly contain glutamate and may act as a neuromodulator through blocking the NMDA receptor and also inhibiting nNOS in the rat hippocampus[18]. Besides, the axon terminals, agmatine were also localised toperikarya, dendrites and axons in the hippocampal pyramidal cells according to the same study. Agmatine-like immunoreactivity, observed by using electron microscopy,

Table 1 Distribution of agmatine in various tissues of adult male Sprague-Dawley rats

Tissue	Agmatine concentration (ng/g wet weight) ± SEM
Stomach	71.00 ± 10.33
Aorta	57.41 ± 12.74
Small intestine	55.35 ± 9.39
Large intestine	27.86 ± 6.73
Spleen	17.38 ± 3.17
Lung	10.23 ± 2.82
Vas deferens	9.45 ± 2.08
Adrenal gland	6.97 ± 3.29
Kidney	6.45 ± 1.40
Heart	6.03 ± 0.79
Liver	5.63 ± 0.87
Skeletal muscle	5.30 ± 0.72
Brain	2.40 ± 0.60
Testes	2.04 ± 0.22
Plasma (ng/mL)	0.45 ± 0.05

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showed that in perikarya, agmatine formed dense clusters whereas in the axon and axon terminals it was associated with small, synaptic vesicles proposing that agmatine was a released molecule[8,19].

Considering the given distribution of agmatine in the brain, it can be accepted that agmatine may be responsible for controlling visceral and neuroendocrine processes as well as several CNS functions such as emotions, pain, perception and cognition[8].

The physiological role of endogenous agmatine is yet to be determined. However, there have been compelling studies identifying the neural functions of exogenous agmatine, in particular pathologies or conditions that have put forward the potential therapeutic importance of exogenous agmatine.

Agmatine has a variety of pharmacological effects, most of which are in the CNS. It has been well studied and reported that systemic administration of agmatine prevents all naloxone-precipitated withdrawal signs in morphine-dependent rats in a dose-dependent manner[18], prevents tolerance development to morphine[18,20–23], provides analgesia in an acute pain model, reduces thermal and mechanic hyperalgesia in a neuropathic pain model[24,25] and exerts anti inflammatory activity[26]. It has also been reported that agmatine has anticonvulsant[27,28], neuroprotective[29–31], antistress, anxiolytic and antidepressant activity potentials[32–34]. Additionally, agmatine has been known to have certain neuromodulatory effects on insulin secretion from pancreatic β-cells[35], luteinising hormone-releasing hormone and gastrin secretion from hypothalamus[36] and inhibition of vasopressin[37]. It was also recently shown that agmatine exhibits orexigenic activity when administrated to the hypothalamic paraventricular nucleus resulting in increased feeding in a dose-dependent manner[38].

Considering the given comprehensive pharmacological effects of agmatine, its role in cognition has not been extensively investigated. However, now there is accumulating evidence of that agmatine having noticeable effects on learning and memory in experimental animal models. The main purpose of this review is to discuss the biological role/therapeutic potential of agmatine on cognitive functions/deficits based on published research studies.

Role of endogenous agmatine in cognition

It has been shown by several studies that endogenous agmatine plays a physiological role in learning and memory in a variety of cognitive tasks proposing agmatine levels in rats brain are elevated within the learning process[39,40].

Initial studies focusing on the L-arginine/arginase pathway in ageing reported that there were significant increases in total NOS activity especially in the hippocampus, perirhinal, postrhinal and temporal cortices and total arginase activity in the perirhinal cortex of the aged rats with impaired spatial learning and object recognition memory. These data revealed an age-related involvement of arginase and NO/NOS pathways in learning and memory leading to investigation of endogenous agmatine's possible effect on learning and memory[41].

In a study examining the age-related alteration of agmatine levels in memory-associated structures of rats brain, showed that agmatine significantly decreased in the CA1, but increased in the CA2/3 and dentate gyrus, subregions of the hippocampus in aged and middle-aged rats. In aged rats, agmatine levels were found to decrease in the prefrontal cortex, and on the other hand, increase in the entorhinal, perirhinal, postrhinal and temporal cortices[42].

A previous study investigated the rats brain levels of agmatine in spatial learning. It was revealed that spatial learning resulted in region-specific elevation of agmatine levels, suggesting that agmatine might be involved in the processes of learning and memory. Morris water-maze task was used to assess spatial learning and memory and agmatine levels were shown to significantly increase by using liquid chromatography/mass spectrometry in the water-maze training group in the CA1 and dentate gyrus subregions of the hippocampus, the entorhinal cortex and the vestibular nucleus when compared with the non-training groups. These results demonstrated that spatial learning induced region-specific elevation of agmatine, and raised a novel issue of the involvement of agmatine in the processes of learning and memory[39].

In 2009, the brain levels of L-arginine and its other metabolites in addition to agmatine, L-citrulline and L-ornithine were also investigated for the possible changes of their brain levels in spatial and non-spatial learning in the T-maze task. The results showed a region-specific elevation of L-citrulline and agmatine brain levels in T-maze training groups relative to the control group[43].

In a most recent study, dynamic changes of extracellular agmatine were examined in the rat's dorsal hippocampus in the water-maze task by using the *in vivo* microdialysis technique coupled with highly sensitive liquid chromatography/mass spectrometry assay. Microdialysis sampling was conducted before, during and after water-maze training to find a hidden platform on the first and fourth day of testing. It was shown that the more dramatic rise was observed in extracellular agmatine in the dorsal hippocampus, the faster water-maze task was learned in animals. It was demonstrated that water-maze training induced increase in extracellular agmatine in the dorsal hippocampus (the basal level was doubled after three days of training), suggesting that endogenous

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agmatine plays a role in the spatial learning and memory processes and a crucial role in the initial phase of encoding and processing information retrieval[40].

Pharmacological role of agmatine in cognitive functions/deficits

In early 2000s, the effect of exogenous agmatine on learning and memory has been examined in a variety of tasks, such as fear conditioning (contextual and cued conditioning), water maze, inhibitory avoidance and object recognition[12,44–47].

In 2000, Stewart and McKay[44] examined agmatine's effect on hippocampus-related learning and memory in contextual fear conditioning. According to their results, agmatine disrupted both the acquisition and early consolidation of contextual fear stimuli suggesting that polyamine modulation of NMDA receptors most likely within the hippocampus is required for contextual learning, since high levels of agmatine are known to be able to inhibit the NMDA receptor activity[44].

Two years later in a different study but with similar results, agmatine was shown to have no effect on finding the hidden platform in the water-maze task and to cause a dose-dependent impairment in contextual learning and to have not improved auditory-cued learning in the fear conditioning[48].

In the same time, Arteni et al.[47] conversely found that systemic administration of agmatine facilitated memory consolidation in a dose-dependent manner (0.1, 1, 10 and 20 mg/kg) in the inhibitory avoidance task. According to the findings of this study, agmatine facilitated memory consolidation when it was administrated immediately after the training session (24 h before the test session), whereas it showed no effect when administrated 1 h before the test session. Since the inhibitory avoidance task is considered to be based on amygdala-related learning, it was suggested that effect of agmatine on memory consolidation might be mediated through noradrenergic mechanisms by the activation of the locus coeruleus[45].

Liu et al.[49] demonstrated that intracerebroventricular (i.c.v.) administration of agmatine at a relatively low dose of 10 μg improved the animals' performance in the standard radial arm maze by providing fewer errors in the working, but not in the reference memory. Additionally, rats significantly spent more time to explore displaced objects in the object recognition memory task[49].

In a study investigating agmatine's effect on either working or reference memory in water-maze tasks when administered through i.c.v. microinfusion, it revealed that agmatine improved spatial working memory but not reference memory suggesting agmatine might have a differential effect on these two types of spatial learning and memory[50].

The behavioural effects of pre-test agmatine treatment in water-maze, T-maze and object recognition tasks with low and high doses (1 and 40 mg/kg, intraperitoneally) were evaluated in a different study. It was shown that low and high doses of agmatine significantly reduced the time to reach the previous platform location without affecting the swimming speed. Additionally, high-dose agmatine provided an increase in the percentage of time spent in the target quadrant with the longer retention time[51]. Interestingly, pre-test treatment of agmatine facilitated the reference memory in the water maze under the condition of the longer retention interval unlike the previous studies. In the same study, agmatine treatment did not affect memory involved in object recognition, but facilitated the response to displacement of the familiar objects, and it is known that 'object/place' memory is related to the medial temporal lobe structures, perirhinal cortex and hippocampus[51].

Agmatine plays an important role in regulating intracellular polyamine content. Physiological concentrations of putrescine, spermidine and spermine are essential for maintaining normal cellular function[52]. It was found that decreased putrescine synthesis in dentate gyrus, a subregion of hippocampus, resulted in anxiety-like behaviour and impaired memory for the object displacement. Recently, it has been claimed that putrescine levels in dentate gyrus have increased following agmatine treatment. It is therefore possible that the facilitating behavioural effect of agmatine may also be associated with its modulatory roles in the polyamine system and hippocampal neurogenesis[53].

Since central cholinergic activity plays a crucial role in learning and memory, scopolamine, a muscarinic receptor antagonist, known to induce cognitive impairment especially through hippocampal mechanisms, has been recently used in studies concentrating on the effect of agmatine on hippocampus-related cognitive deficits[12,54].

In this regard, a recent study investigated the effect of agmatine on scopolamine-induced cognitive impairment. It was revealed that agmatine dose dependently reduced scopolamine-induced cognitive deficits in passive avoidance and in three-panel runway tests. The results also showed that agmatine did not affect learning and memory when given alone. Consequently, it did not have an effect on reference memory but improved the impaired reference and working memory in the three-panel runway test and emotional memory in the passive avoidance test[12]. In a different study, agmatine pre-treatment prevented both scopolamine-induced deficits in water-maze performance and inactivation of hippocampal molecular signalling pathways involved in learning and memory, such as extracellular regulated kinases and Akt, a serine/threonine kinase[54].

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The neuroprotective potential of agmatine has been detected in a Parkinson's disease model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (i.n. 1 mg per nostril). Agmatine has shown to attenuate dopaminergic cell loss in substantia nigra pars compacta and repeated treatment (30 mg/kg i.p.) improved short-term memory displayed by MPTP in aged mice. Observed behavioural benefits of agmatine were accompanied with the prevention of MPTP-induced decrease in hippocampal glutamate uptake. That means, one possible mechanism by which agmatine exerting its neuroprotective effects against MPTP neurotoxicity may be due to the modulation of glutamate reuptake into neurons, the main mechanism responsible for decreasing extracellular glutamate levels, thus attenuating glutamate neurotoxicity[55].

Amyloid beta fragment 25–35 ($A\beta_{25-35}$), the neurotoxic component of the full length $A\beta_{1-42}$, which has an essential role in the pathogenesis of Alzheimer's disease, is known to cause memory deficits in rodents. It was reported that agmatine significantly decreased $A\beta_{25-35}$-induced spatial learning and memory impairment in different tasks including water-maze, radial arm-maze and the object recognition tests suggesting agmatine has a considerable neuroprotective effect[56]. Supportively, agmatine was shown to prevent lipopolysaccharide (LPS)-induced spatial memory impairment in the water-maze task and also to decrease in hippocampal caspase-3 activation, an indicator of neuronal apoptosis, induced by LPS[47].

Since ageing itself is a major process that causes cognitive impairments and NO is known to play a crucial role in that process, agmatine therefore was examined in aged rats for its improving effects on behavioural functions and age-related changes in the NOS activity. It was found that in aged rats, spatial working memory in the water-maze task and object recognition memory significantly improved by agmatine treatment (40 mg/kg, i.p.), whereas exploratory activity and spatial reference memory were not affected. Additionally, agmatine attenuated the age-related elevation in total NOS activity and restored eNOS protein to its normal level[57].

It has been recently investigated how chronic administration of agmatine (40 mg/kg i.p. once daily) in 4–6 week period affected behavioural function and neurochemistry in aged rats. Aged rats treated with saline displayed impairment in spatial learning and memory in the water maze and object recognition memory relative to young rats. On the other hand, prolonged agmatine treatment improved animals' performance in the reversal test of the water maze, T-maze and object recognition memory tests, and significantly suppressed age-related elevation in NOS activity in the dentate gyrus of the hippocampus and prefrontal cortex. However, this prolonged supplementation was unable to improve spatial reference learning and memory in aged rats, which is consistent with the previous studies[58].

The improving effects of agmatine on cognitive dysfunctions were also examined in streptozotocin-induced memory deficits in diabetic rats using the Morris water maze and object recognition paradigm. It was shown that chronic treatment with agmatine (5–10 mg/kg, i.p. for 30 days) improved cognitive performance, which was shown to be impaired 30 days after diabetes induction in diabetic groups, and additionally lowered hyperglycaemia, oxidative stress, and cholineesterase activity. Moreover, agmatine's effect on cognition was suggested to be independent from adrenal imidazoline-2 receptors, because of agmatine's demonstrated effect in adrenalectomised rats[59].

Agmatine was also shown to inhibit morphine-induced memory impairment in the step-down inhibitory avoidance test in mice. It was administered before and after training and after the test, separately and it was found that agmatine (5, 10 and 20 mg/kg, s.c.) facilitated memory formation and retrieval, without an effect on memory consolidation. The effect of agmatine was reversed by pre-training and pre-test administration of idazoxan, an imidazoline receptor antagonist, suggesting that the effect of agmatine on memory formation might be mediated through activation of imidazoline receptors[60].

Discussion

The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. Animal care was in accordance with the institution guidelines.

As discussed above, agmatine, a putative neurotransmitter, has been suggested to participate in physiological learning and memory. When administered exogenously, it may have an improving effect on cognitive deficits present in certain pathological conditions as well as in ageing.

Ageing is a process, causing cognitive impairments and oxygen free radicals have been proposed to be responsible for abnormal cell function and cell death, therefore resulting in ageing. Among these free radicals, NO has been suggested to have an essential role in the ageing process due to its excessive amounts exerting neurotoxic effects on the brain[41,61].

NO is generated from L-arginine by NOS. There are three isoforms of NOS: nNOS is responsible for synaptic plasticity, learning and memory, whereas eNOS provides the stabilisation and regulation of the vascular microenvironment that also contributes to neuroplasticity[57]. iNOS, on the other hand, is produced in response to pathological conditions[41].

Given a number of studies investigating the contribution of NO/NOS activity and/or the L-arginine

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metabolic pathway in the ageing process[57,62], it revealed that total NOS activity tends to significantly increase in aged rats brain and it is correlated with the cognitive impairments[41,63]. Agmatine, as a competitive inhibitor of both nNOS and iNOS[14] but conversely a stimulator of eNOS[16], was suggested to improve cognitive functions in an age-dependent manner[57]. Agmatine's facilitating effects on learning and memory is also attributed to its stimulatory effect on eNOS, which is responsible for stabilising the vascular microenvironment and therefore is vital for synaptic plasticity, learning and memory[51]. In addition, various studies have shown that agmatine's neuroprotective effect is shown to contribute its cognitive enhancing effects[47,56]. Agmatine reverses neuroinflammation and memory deterioration induced by LPS. Given the fact that LPS increases iNOS activation, and therefore NO production, agmatine prevents LPS-induced memory deficits possibly by iNOS inhibition[47].

On the contrary, earlier studies claimed that agmatine's impaired effect on cognitive functions was attributed to its inhibitory nature on NMDA receptors and NO which are important in learning and memory[44,48].

The central cholinergic system plays a crucial role in learning and memory. Therefore studies targeting cognitive functions have used scopolamine, a muscarinic receptor antagonist to induce memory impairment and to investigate how the cholinergic system is involved in the cognition process[12,54,64]. Agmatine has been shown to reverse scopolamine-induced learning and memory impairment. Although glutamatergic system activity is necessary for cognition, increased glutamate levels or NMDA activity is suggested to participate in scopolamine-induced learning and memory impairment[65]. Additionally, scopolamine treatment is shown to display a significant decrease in NOS activity, and increase in arginase activity, L-ornithine and putrescine levels in the DG subregion of the hippocampus[64]. Since agmatine blocks NMDA receptors and has a modulatory effect on NO/NOS and L-arginine pathways, its preventing effect on scopolamine-induced learning and memory may be attributed to its NO/NOS and L-arginine modulation as well as NMDA receptor antagonism, therefore suppressing excessive glutamatergic activity[54,64]. Additionally, agmatine is shown to prevent morphine-induced memory impairment and imidazoline receptors are suggested to be involved in this effect[60].

Conclusion

Taken together, accumulating evidence demonstrates that endogenous agmatine is involved in the learning and memory process and administration of exogenous agmatine has considerable improving effects on cognitive impairment. The underlying mechanisms of agmatine's enhancing effect on learning and memory have been investigated through the NO/NOS pathway, NMDA and imidazoline receptors, polyamine metabolism and cholinergic system, especially in conditions such as ageing and neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases coupled with impaired cognition. Agmatine might be accepted as a future therapy for cognitive disorders; however, the exact mechanism of agmatine's effect on learning and memory remains unclear at present. Further studies should be addressed to understand the underlying mechanism of both physiological and pharmacological agmatine's effects in learning and memory.

Abbreviations list

ADC, arginine decarboxylase; CA, cationic amine; CNS, central nervous system; eNOS, endothelial nitric oxide synthase; i.c.v., intracerebroventricular; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA, N-methyl-D-aspartate; NOS, nitric oxide synthase; nNOS, neuronal nitric oxide synthase.

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