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REVIEW PAPER

Therapeutic Effect of Agmatine on Neurological Disease: Focus on Ion Channels and Receptors

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Abstract

The central nervous system (CNS) is the most injury-prone part of the mammalian body. Any acute or chronic, central or peripheral neurological disorder is related to abnormal biochemical and electrical signals in the brain cells. As a result, ion channels and receptors that are abundant in the nervous system and control the electrical and biochemical environment of the CNS play a vital role in neurological disease. The *N*-methyl-D-aspartate receptor, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor, kainate receptor, acetylcholine receptor, serotonin receptor, α2-adrenoreceptor, and acid-sensing ion channels are among the major channels and receptors known to be key components of pathophysiological events in the CNS. The primary amine agmatine, a neuromodulator synthesized in the brain by decarboxylation of L-arginine, can regulate ion channel cascades and receptors that are related to the major CNS disorders. In our previous studies, we established that agmatine was related to the regulation of cell differentiation, nitric oxide synthesis, and murine brain endothelial cell migration, relief of chronic pain, cerebral edema, and apoptotic cell death in experimental CNS disorders. In this review, we will focus on the pathophysiological aspects of the neurological disorders regulated by these ion channels and receptors, and their interaction with agmatine in CNS injury.

Keywords Agmatine · Ion channels · Receptors · Neurodegenerative disease · Receptor blockade

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Abbreviations

CNS	Central nervous system
PNS	Peripheral nervous system
AD	Alzheimer's disease
PD	Parkinson's disease
HD	Huntington's disease
ADC	Arginine decarboxylase
ROS	Reactive oxygen species
NF-κB	Nuclear factor kappa B
TBI	Traumatic brain injury
NO	Nitric oxide
SCI	Spinal cord injury
BMP	Bone morphogenetic protein
Aβ	Amyloid-beta
Nrf2	Nuclear factor (erythroid derived 2)-like 2
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MES	Maximal electroshock seizures
PTZ	Pentylenetetrazole
NMDAR	*N*-Methyl-D-aspartate receptor
AMPAR	α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor
NOS	Nitric oxide synthase

KAR	Kainite receptor
GPCR	G protein-coupled receptor
CDS	Clonidine displacing substance
AChR	Acetylcholine
mAChR	Muscarinic acetylcholine receptor
nAChR	Nicotinic acetylcholine receptor
5-HT	5-Hydroxytryptamine
VDCC	Voltage-dependent calcium channel
LVA	Low-voltage activated
HVA	High-voltage activated
ENaC/DEG	Epithelial Na^+ channel/degenerin
ASIC	Acid-sensing ion channel
EL/IL	Extracellular/intracellular loops

Introduction

Ion channels and receptors are the macromolecular membrane pores that traffic a series of ions (Na^+, K^+, Ca^{2+}, Cl^-) and chemicals (neurotransmitters, hormones etc.) in or out of the cells and propagate the biochemical and electrical signals. Functional initiation of ion channels requires stimuli such as ligand binding, chemical/mechanical changes, and altered membrane potentials. Therefore, any iatrogenic, autoimmune, toxic, or genetic dysfunction can cause ion channel-related diseases termed channelopathies, which overlap with acute and chronic neurodegenerative disorders such as ischemic stroke, traumatic injury, epilepsy, Alzheimer's disease (AD), schizophrenia, and Huntington's disease (HD) [1]. The majority of neurodegenerative diseases are related to cell death caused by disrupted ion channels and receptors or metabolic functions of neuronal cells [2–5]. In the healthy brain, ionic homeostasis is a major component of neuronal information transmission via action potentials, which are also related to synaptic transmission between presynaptic and postsynaptic neurons. Loss of synaptic function due to low energy supply in neurodegenerative disorders leads to attenuation of ion homeostasis [6, 7]. In the diseased brain, ion homeostasis is maintained by a series of ion channels in brain cells, predominantly in neuron, astrocyte and microglia, and a myriad of ions that are transported across the cell membrane via those channels (Table 1). Among the range of associated ions, potassium, sodium, chloride, and calcium collectively play a pivotal role in cellular damage [1, 8]. Following central nervous system (CNS) injury, the well-orchestrated ion exchange across the membrane via ion channels or receptors is disrupted and brain cells lose their normal function, leading to death.

Agmatine, an arginine-derived primary amino acid found in the nerve cell body and synaptic terminals, acts as

Table 1 Major ion channels and receptors to which agmatine act as a ligand and modulates their functions

Ion channel/receptor	Ligand	Conducting ions	Related neurological disorders	References
NMDA	L-Glutamate, NMDA, glycine	Na^+, Ca^{2+}, K^+	Stoke and traumatic injury, AD, HD, pain, schizophrenia, depression	[38, 131, 133, 134]
AMPA and kinate	L-Glutamate, AMPA	Na^+, K^+, less Ca^{2+}	Stoke and traumatic injury, AD, epilepsy schizophrenia, depression, amyotrophic lateral sclerosis, autism	[98]
α2-Adenoceptor: imidazoline receptors	α2-Adenoceptor: epinephrine norepinephrine, α-methyl DOPA and others Imidazoline receptors: imidazoline compounds	α2-Adenoceptor : K^+, Na^+ and H^+ Imidazoline receptor: Ca^+	Pain, panic disorder, addiction, depression, anxiety, hypertension	[164–172]
AChR	Acetylcholine nicotine	Na^+, Ca^{2+}, K^+	Myasthenia gravis, epilepsy, AD, PD, schizophrenia, Tourette's syndrome, idiopathic inflammatory bowel disease, addiction, anxiety, depression	[57, 60, 62–64]
VDCC	Membrane potential	Ca^{2+}	Epilepsy, seizures, AD, pain, autism spectrum disorder, migraine, anxiety, depression	[77, 78, 80]
ASICs	Extracellular protons	Na^+, less Ca^{2+}	Ischemic stroke, traumatic injury, pain, HD, PD, multiple sclerosis, glioblastoma, epilepsy	[88, 92, 99, 120]
Serotonin (5-HT)	Different serotonergic compounds	Na^+, Ca^{2+}, K^+ by 5-HT3	AD, anxiety, depression, seizure locomotor activity, aggression	[107, 108, 130, 169]

a neuromodulator that mimics the functional properties of other neurotransmitters [9, 10]. The enzyme arginine decarboxylase (ADC) synthesizes agmatine by decarboxylation of L-arginine [11]. On the other hand, studies suggested that in the mammal lacking ADC, decarboxylation of L-arginine is catalyzed by the ornithine decarboxylase enzyme. Agmatine-expressing cells have been found in all regions of the brain such as the hypothalamus, frontal cortex, striatum, medulla, hippocampus, and locus coeruleus along with measurable ADC activity [9, 10, 12–16]. However, the highest number of these cells was observed in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus, which also exhibited the highest ADC activity. Diverse mechanisms of neuroprotection by agmatine in response to neurodegenerative diseases have been reported by many research groups, such as blocking of harmful ion channels, suppressing harmful reactive oxygen species (ROS), promoting neurogenesis, angiogenesis, reducing glial scars etc [17–20]. In a recent review, Laube and Bernstein preciously reviewed the recent studies about the agmatine metabolism and clinical application including nervous system [21]. In acute brain diseases, both exogenous and endogenous (via overexpression of ADC or down regulation of agmatinase experiments etc.) agmatine were reported to be effective in reducing hypoxic brain tissue damage [17, 20, 22–26]. The exogenous agmatine is also reported to be an anti-proliferative agent which reduces the biosynthesis and increases the degradation of the cell growth and proliferative polyamines such as putrescine, spermidine and spermine in different cancer cell lines [27, 28]. Exogenous agmatine treatment also can inhibit advanced glycation end products formation in diabetic kidney [29]. Over the last few decades, a significant number of studies have been performed regarding the interacting targets of both endogenous and exogenous agmatine in the brain and other systems. Agmatine interacts with the different receptors and ion channels of the brain cells which are responsible for different neurodegenerative diseases. Here, we will discuss the association of the different ion channels and receptors responsible for various neurodegenerative diseases and their possible relationship with agmatine.

Medicinal Chemistry of Agmatine

The primary amine agmatine is produced from the L-arginine by the enzyme ADC. This decarboxylated arginine, agmatine can be found naturally in herring sperm, octopus muscle, ergot fungi, ragweed pollen, and also in mammalian brain [11]. Structurally agmatine has a protonated guanidine group and an amino group. At the physiological pH, agmatine can act as a divalent cation due to these protonated groups. On the other hand, due to the presence of the additional carboxylate group, arginine acts as a net monovalent cation [30]. Agmatine is also suggested to behave as monovalent when it interacts with the microscopic channels and divalent as a macroscopic charge transfer [30].

Agmatine can be metabolized into putrescine by the enzyme agmatinase or oxidized into γ-guanidinobutyraldehyde by diamine oxidase (Fig. 1). Agmatinase belongs to the family of hydrolases, those acting on carbon–nitrogen bonds other than peptide bonds, specifically in linear amidines, then synthesizes putrescine, one of polyamines. Putrescine is metabolized further into the polyamines, spermidine and spermine [31]. On the other hand, diamine oxidase deaminates oxidatively diamines to produce aldehydes, ammonia and hydrogen peroxide. Therefore, the amino group of agmatine is metabolized by the action of diamine oxidase to become γ-guanidinobutylbutylic acid-aldehyde, and is further metabolized to γ-guanidinobutyric acid by aldehyde dehydrogenase (Fig. 1). Agmatine has two reactive groups, which increased its possibility of various chemical reactions in vivo. With this potentiality for biochemical reactions, agmatine has been used as an experimental and investigational drug in different neurological disorders. However, the precise mechanism of action for its potential clinical indications has not been identified yet.

Target Ion Receptors/Channels of Agmatine

Electrical and chemical signals in neurons are orchestrated by the neurotransmitters, ion channels, receptors, and the electrochemical gradient. In this manner, neurons can communicate with each other and other cells in the brain, which is essential for normal brain function. In the healthy brain, agmatine is known to be a neuromodulator that regulates multiple neurotransmitters and signaling pathways. It has also been demonstrated to exert neuroprotective effects, which are likely due to the interaction between the membrane receptors/channels and agmatine, in various neuronal pathologies. However, the mechanism underlying the interaction between agmatine and the membrane receptors/channels remains unknown in both the healthy and diseased brain. Therefore, we will discuss the major ion channels and receptors associated with various brain functions and disorders, and their association with agmatine.

N-Methyl-D-Aspartate Receptor (NMDAR)

NMDARs, the glutamate-gated channels permeable to calcium, sodium, and potassium, are crucial for CNS development, cognitive function, locomotion, and breathing. NMDARs are activated by the excitatory neurotransmitter glutamate and are also a key component of many CNS related major acute and chronic pathological conditions such as stroke, TBI, PD, AD, pain, depression, schizophrenia

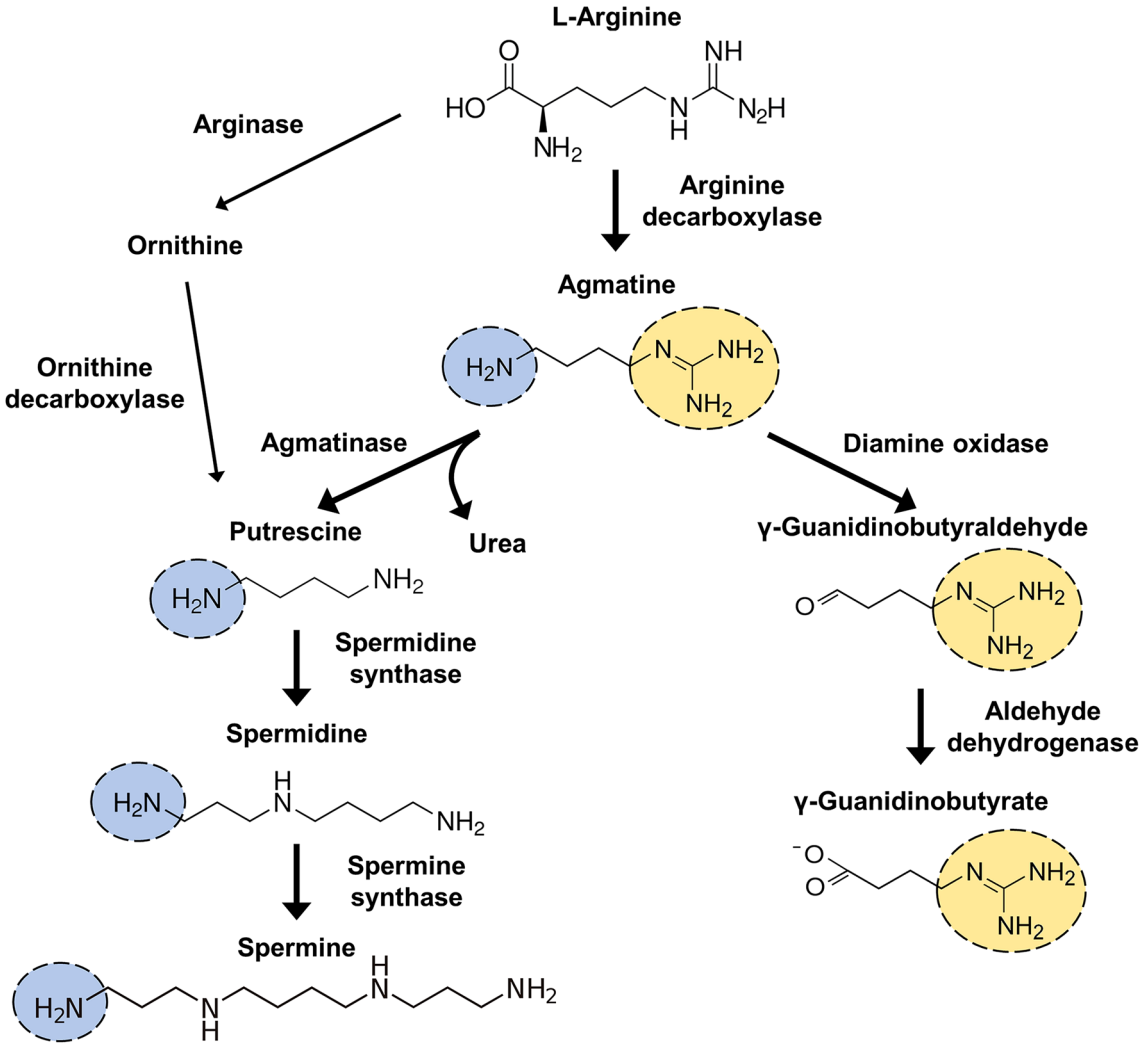

Fig. 1 Synthesis and metabolism of agmatine. Agmatine is synthesized from the L-arginine by arginine decarboxylase (ADC). Agmatine structurally contains two protonated groups, a guanidine group and an amino group, and thus can act as a divalent cation in the physiological pH. The guanidine group of agmatine is metabolized by diamine oxidaze and the amino group is metabolized by agmatinase to γ-guanidinobutyraldehyde and putrescine respectively

etc. [21, 32, 33]. A typical heteromeric NMDAR consists of four subunits, two NMDAR1 and two NMDAR2 (A–D), and may also contain a less common subunit, NMDAR3 (A, B) [34]. NMDAR3 is expressed in neurons of various different regions of the brain according to the developmental age. Among the seven distinct subunits, NMDAR2 determines the functional heterogeneity of the NMDAR. Each NMDAR subunit has a large extracellular amino-terminal domain, which includes the ligand binding site, connected to four helical transmembrane domains that form the ion channel, and the transmembrane domain connects to the short intracellular carboxyl-terminal domain [34]. NMDAR can be found in both neuronal and glial cells. In a neuron, NMDARs are synaptic or extra-synaptic according to their localization and the majority of the synaptic NMDARs are located post-synaptically. NMDARs are associated with both survival and death mechanisms of neurons in neurodegenerative diseases. In the diseased brain, the extracellular glutamate increase over-activates the NMDARs, resulting in elevated Ca^{2+} and Na^{+} influx into the cell which triggers NMDAR-mediated neuronal excitotoxicity (Fig. 2a) [35]. After ischemic injury, NMDAR over-activation also produces NO by activating nitric oxide synthase (NOS), which is a major mediator of neuronal death [36, 37]. As a result, controlling neuronal excitotoxicity and inhibition of NO production via modulation of NMDAR function is a first line treatment choice for ion channel-related brain disorders. The primary amine agmatine has been reported to be a neuroprotective agent by modulating NMDARs, the NO pathway, and oxidative stress in various neurodegenerative diseases

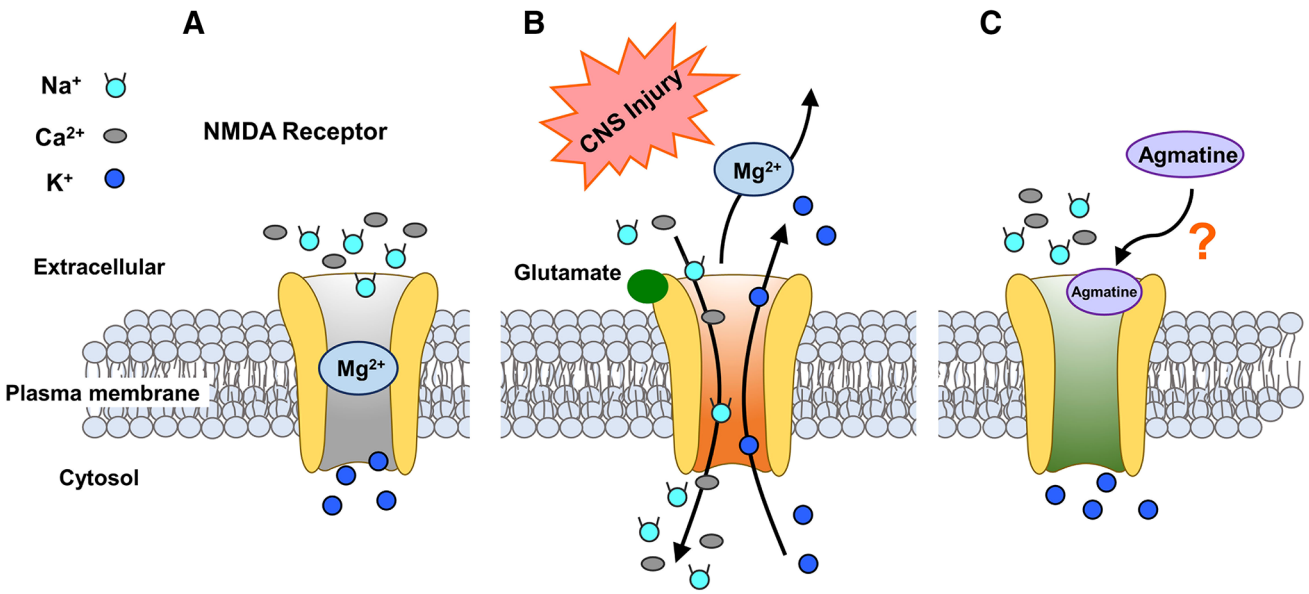

Fig. 2 Agmatine inhibits NMDAR activation. **a** at resting stage the pore of the NMDAR is blocked by magnesium ion. **b** In brain injury excessive glutamate release over-activate the NMDAR and transports the ion in and outside of the cell which causes Ca^{2+} excitotoxicity. **c** NMDA antagonist agmatine inhibits ionic transport via NMDAR and attenuates the Ca^{2+} excitotoxicity

[18, 23, 38, 39]. Agmatine treatment in the different neuronal cultures have been demonstrated to be neuroprotective against excitotoxicity by blocking NMDAR and inhibiting the increase in cellular calcium levels (Fig. 2b) [18, 40, 41]. Agmatine inhibits NMDA excitotoxicity-induced cell death, but not by intercellular Ca^{2+} or protein kinase blockade [41]. Differential studies on synaptic and extrasynaptic NMDARs have suggested that synaptic NMDARs were more neuroprotective, whereas the extrasynaptic NMDARs induced cell death, and increase in neuronal NO [18, 42–44]. In various neuropathologies, neuronal death by NO synthesis was also attenuated by the NMDA antagonist agmatine via inhibition of NOS [45]. Previous studies also reported that endothelial NOS was attenuated by agmatine in cerebral ischemia in rats [23, 38]. Although a number of studies have explored the relationship between NMDAR and agmatine, determination of the full molecular interaction between these two could be an important finding in the treatment of various neurological disorders.

Non-NMDA Receptors

According to the agonist preference, the non-NMDA receptors are divided into two subclasses; α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs) and kainite receptors (KARs). Among all ionotropic and glutamate receptors, AMPARs are known for fast excitatory synaptic transmission and are densely dispersed in the mammalian brain, whereas KARs are generally copious in the least abundant NMDAR pathways. Both AMPAR and KAR are tetrameric and comprise GluA (1–4) and GluK (1–5) subunits, respectively [46, 47]. A high proportion of AMPARs and few KARs are impermeable to Ca^{2+}. However, Ca^{2+}-permeable AMPARs and KARs can regulate neurological disease processes in a similar manner to NMDARs [48, 49]. Ca^{2+}-permeable AMPARs are typically expressed in hippocampal CA1 regional pyramidal neurons, and the increase in the number of AMPARs in the diseased brain indicates that they are of marked importance. A high number of AMPARs can decrease the vulnerability of the ischemic neurons, but a low number of AMPARs increases the vulnerability [50, 51]. Due to the higher excitotoxicity of NMDARs and AMPARs, the role of the KARs in excitotoxic cell death have received less focus. Of the five subunits of the KAR, GluK4 and GluK5 exhibit high agonist-affinity, and GluK4 is co-expressed pre-and post-synaptically with GluK2 in the CA3 region of the hippocampus, whereas the remaining subunits are expressed throughout the CNS [52, 53]. Both AMPARs and KARs follow the same intracellular Ca^{2+} loading mechanism of cell death during ischemia, but it remains unclear whether Ca^{2+} overload is the sole reason for cell death. Koh et al. demonstrated that the divalent cation, Zn^{2+}, to which AMPARs are permeable, contributes to neuronal death via mechanisms such as poly ADP ribose polymerase activation, generation of ROS, and enzyme induction [54]. However, the pro-apoptotic c-Jun N-terminal kinase signaling cascade can be activated by over activation of the KAR subunit GluK2 in the ischemic brain [55]. The effect of agmatine on AMPARs and KARs has not been explored to the same extent as that on NMDAR. However, Neis et al.

reported that agmatine has potential antidepressant properties via activation of AMPARs [56]. In their study, they found that the pretreatment of the agmatine (0.1 mg/kg oral) reduced the immobility time than the AMPAR antagonist treated mice in tail suspension tests. The pretreatment of the agmatine also increased the synaptic GluA1 and PSD95 protein expression and activated the PI3K/Akt/mTOR pathway. They suggested that the antidepressant effects of agmatine resemble the antidepressant effects of ketamine.

α2-Adrenoreceptor/Imidazoline Receptor

Both the imidazoline receptor and the α2-adrenoreceptor are well-known components of the sympathetic nervous system, and their agonist have been used as a common drug to treat hypertension, pain and panic disorders, addiction, depression, and other behavioral disorders. However, due to difficulties regarding distinction of the functional properties of the α2-adrenoreceptor and the imidazoline receptor, researchers focused on the agents or endogenous ligands that could selectively identify the receptors and bind to them. The α2-adrenoreceptors are a family of G protein-coupled receptors (GPCRs) that can be found in both the CNS and the PNS and are pharmacologically divided into three subclasses: α-2A (CNS, sympatholytic), α-2B (blood vessels, vasodepressor), and α-2C (CNS, sympatholytic) [57]. Structurally, the α2-adrenoreceptor has three extracellular domains (with small amino termini) and three intracellular domains (with large carboxy-termini), and the hydrophobic transmembrane domain consists of seven well-conserved helices (Fig. 3a) [58]. Henderson et al. suggested that these membrane spanning transmembrane domains form a pocket-like structure, which serves as the ligand binding site for the adrenoreceptors [58, 59]. The notion of imidazoline receptors evolved while searching for the anti-hypertensive function of clonidine, an imidazoline compound, which was first thought to be a peripheral α2-adrenoreceptor agonist. However, recent studies suggested that the anti-hypertensive function of clonidine and other imidazole-possessing ligands occurred via interaction with an imidazoline receptor rather than binding to the α2-adrenoreceptor [60]. Several imidazoline-like drugs have been developed, which selectively bind to the imidazoline receptors but have no affinity for α2-adrenoreceptors. The imidazoline receptors have been identified as three distinct classes: I-1, I-2 (I-2A, I-2B), and I3. The I-1 receptors regulate the sympathetic inhibitory functions of the sympathetic nervous system and regulate the systolic and diastolic blood pressure by reducing the peripheral resistance, and have been well-studied. The functions of the I-2 receptors are yet to be determined, but are suggested to be an important therapeutic target for pain and stroke [61, 62]. The I-3 receptors induce insulin secretion from pancreatic β cells. Agmatine

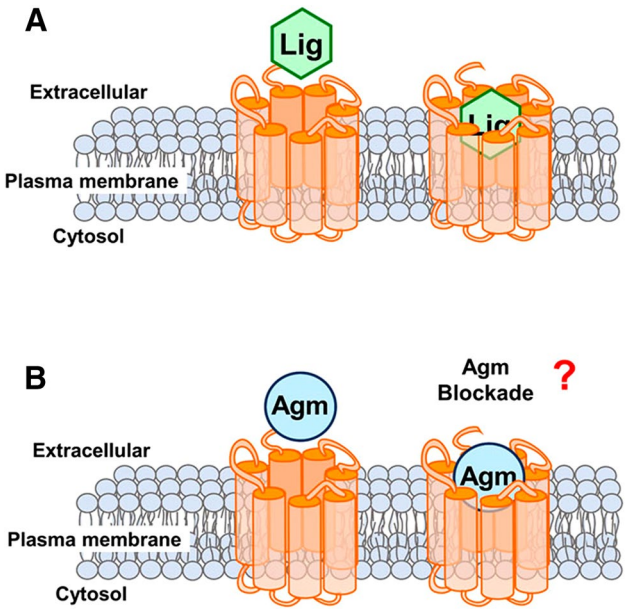

Fig. 3 Probable binding site for agmatine in GPCR types. **a** The transmembrane domain of GPCR types produce a channel for ion transport which also possess the ligand binding site. **b** Probable mechanism of GPCR blockade by agmatine (Lig: ligand, Amg: agmatine)

was first purified as a clonidine displacing substance (CDS) from the α2-adrenoreceptors and named CDS by Atlas et al. [63]. Others later found that it also displaced imidazoline binding from I-1 and I-2 receptors [12, 64, 65]. Li et al. first reported the notion that the previously identified CDS was agmatine and could be formed in mammalian tissues [12]. Agmatine is considered to have therapeutic potential for treating pain, ischemic injury, and seizures. It has been suggested to regulate morphine-induced analgesia in SCI via a neuronal NOS-dependent mechanism involving the site-specific imidazoline receptors and α2-adrenoreceptors [42, 66, 67]. In mixed I-1/α2 agonists study showed that the anticompulsive-like effects of agmatine in OCD rodents were significantly related to imidazoline binding sites [68]. The anti-depressant, anti-convulsant, and memory retrieval effects of agmatine have been found to be associated with α2-adrenoreceptors in addition to NMDAR and NO [69–71]. The imidazoline receptors I-1/I-2 also interact with agmatine and reduce ethanol-induced anxiolysis, opioid withdrawal anxiety, and depression in mammals. Agmatine has greater potential to reduce morphine dependency than do other I-1-specific ligands such as moxonidine and rilmenidine [72–74]. Giusepponi et al. reported that agmatine has higher affinity and greater anti-addiction potential in the triple interaction among the imidazoline receptors I-1 and I-2 and α2-adrenoreceptors than in the double interaction of imidazoline receptors I-1 and I-2 only [75].

Acetylcholine Receptor

Acetylcholine receptors (AChRs) are divided into two groups according to their agonist; muscarinic (mAChR) and nicotinic (nAChR). Most AChRs are the associated with the parasympathetic nervous system. mAChRs are members of the α-branch of class A GPCRs and have five subtypes ($M_{1–5}$) [76]. Although signal transduction via mAChRs is slow, these receptors were reviewed to be key components in several mammalian physiological processes such as smooth muscle contraction, heart rate regulation, glandular secretion, and many CNS functions [77, 78]. All mAChR subtypes are found in the CNS with higher expression in the cortex, hippocampus, and thalamus, but M_1–M_4 can be found in various tissues throughout the body. The extracellular domain of the mAChR binds with their activator (ACh), the intracellular carboxyl-terminal domain of the M_1, M_3, and M_5 subtypes couples with the Gq-G protein, and that of the M_2 and M_4 subtypes couples with Gi/Go-G proteins [79]. The diseases and their pathophysiology related to the particular mAChRs are still poorly known due to the absence of specific small-molecule ligands. However, recent studies reviewed that the mAChRs are related to diseases such as AD, PD, Sjögren's disease, schizophrenia, Chagas' disease, various smooth muscle disorders such as overactive bladder, and chronic obstructive pulmonary disease [80–82]. The ionotropic nAChRs are ligand-gated ion channels found in both the CNS and PNS. Each nAChR is formed by homomeric or heteromeric pentamers from a group of sixteen subunits (α1–α7, α9–10, β1–β4, γ, δ, ε) [83]. nAChRs are also a member of the cys-loop receptor superfamily, which includes 5-hydroxytryptamine (5-HT), γ-aminobutyric acid, and glycine, and shares structural similarities such as two extracellular N- and C-terminal domains, four transmembrane domains, and a large cytoplasmic domain. The quaternary ammonium affinity-labeling test revealed that the quaternary ammonium reagent could only label the α-subunits, which identified these subunits as the primary binding sites for the agonists [84]. nAChRs are expressed in the neuromuscular junction, autonomic ganglia, and synapses of the brain and spinal cord, and can functionally regulate classical neurotransmission (post-synaptic), neurotransmitter release (presynaptic), and second messengers via Ca^{2+} signaling [83, 85]. The neurotransmitter release function of the nAChRs allows them to participate in mammalian cognitive functions such as learning, memory, and attention [86]. Numerous neurological pathologies, such as AD, PD, epilepsy, schizophrenia, and dysautonomia, are associated with nAChRs [87, 88]. In addition to chronic neurological diseases, the central cholinergic system was reviewed to be associated with increased cortical perfusion in cerebral ischemia via impaired ACh synthesis, and mAChRs in particular are associated with alteration of cerebral blood flow via vasodilation [89]. The neuromodulator agmatine can act on both of the AChR subtypes. However, until now, the efficacy of agmatine on nAChRs was more apparent than that on mAChRs. Loring et al. reported that agmatine can act as both a cation and a neuronal receptor antagonist [90]. Nicotine and other psychoactive drugs act on central nAChRs and mediate conditioned place preference, addiction, depression, and anxiety. Even ethanol and morphine withdrawal syndrome has been reported to be attenuated by agmatine [91–96]. Studies suggested that agmatine modulates neuropeptide Y-mediated neurotransmission in the brain to regulate nAChR-related anxiolytic function [97, 98]. Scopolamine-induced learning and memory impairment have been reported to be reversed by exogenous agmatine treatment [99]. Thus, further study of agmatine and AChR function warrants more attention.

Voltage-Dependent Calcium Channel

As a type of voltage-gated ion channel, voltage-dependent calcium channels (VDCCs) are activated by cell membrane depolarization and allow the densely-concentrated extracellular calcium ions to flow into the cell and act as the second messenger of the electrical signals that transduce the membrane potential in various excitable and non-excitable tissues such as cardiac and smooth muscle, neurons, and endocrine tissues. The fundamental activity of VDCCs is to couple the cell surface electrical signals with physiological intracellular processes such as calcium-dependent enzyme and protein modulation, contraction, gene expression regulation, and synaptic transmission. In a review Tsien et al., suggested that VDCCs are divided into two major groups; low-voltage activated (LVA) and high-voltage activated (HVA), according to their activation in response to the membrane potential [100]. Considering the cellular distribution, pharmacology, kinetics, and single channel conductance, the HVAs are classified into L, P/Q, N, and R-types, whereas the LVA has only the T-type transient channel [101, 102]. VDCCs are reviewed to be heteromultimeric and comprise multiple subunits, such as the pore-forming common principal subunit $Cav\alpha_1$ and other ancillary subunits $Cav\alpha_2\delta_{1–4}$, $Cav\beta_{1–4}$, and $Cav\gamma_{1–8}$, but the LVA channels are devoid of ancillary subunits [103]. Each $Cav\alpha_1$ subunit contains four transmembrane domains of six membrane-spanning helices each, S1–S6. Of these, the positively charged amino acids (lysine/arginine) of S4 regulate the voltage-dependent activation of the VDCCs [104]. $Cav\alpha_1$ forms the selective pore for the ions and comprises the drug or ligand binding site. The large carboxy- and short amino-terminal of the $Cav\alpha_1$ subunit are located intracellularly. The different subtypes of VDCCs are associated with different neurological and non-neurological diseases. Neurological diseases related to the VDCC subtypes and drug development targeting those subtypes have been

reported previously, including PD (L, T-types), AD (L-type) epilepsy (T, R-types), pain (L, N, R, T, and N-types), anxiety/dependency (N-types), and febrile seizures (L, T-types) [105–107]. Wang et al., suggested that, although the neuromodulator agmatine does not exert any effect on Na^{2+} and K^{+} currents, it might have some physiological and pharmacological effects on the Ca^{2+} current via VDCC blockade in rat hippocampal neurons [108]. They also suggested that the mechanism underlying VDCC blockade involves reversible blocking of the L-type channel and few other subtypes, and is voltage-dependent [108, 109]. Wang et al. suggested that the presence of agmatine in the presynaptic region of the hypothalamic magnocellular neurons of the SON nuclei and PVN nuclei also regulates VDCCs to modulate neurotransmitter release [110]. The N-type Ca^{2+} channels present in the sympathetic nerve terminals are reported to be inhibited by agmatine treatment, which reduced the intracellular Ca^{2+} and noradrenaline release by the I-2 receptor and eventually reduced the sympathetic vascular tone [111].

Acid-Sensing Ion Channel

The extracellular acidic environment-sensing channels belong to a proton-gated ion channel family known as epithelial Na^{+} channel/degenerin (ENaC/DEG) and termed acid-sensing ion channels (ASICs). ASICs and the other ENaC/DEG super family members share the same topological structures, which comprise a properly organized large extracellular domain rich in cysteine, two hydrophobic transmembrane domains (TM1 and TM2), and small intracellular N and C-termini [112, 113]. The extracellular loop, which spans the TM domains, harbors a pocket-like structure known as an "acidic pocket", and is responsible for the acid-dependent channel gating, desensitization, and response to extracellular regulators [114]. To date, four genes (*ACCN1-4*) have been found that encode six different types of ASIC subunits. The various ASICs function in a range of extracellular pH levels and can be located in both the CNS and PNS, such as ASIC1a (pH 5.8–6.8, CNS, PNS), ASIC1b (pH 6.1–6.2, PNS), ASIC2a (pH 4.5–4.9 CNS, PNS), ASICb (N/A, CNS, PNS), ASIC3 (pH 6.4–6.8, PNS), and ASIC4 (N/A, CNS, PNS) [115, 116]. Structurally, ASICs are trimers and can be both homomeric and heteromeric, e.g., homomeric ASIC1a and heteromeric ASIC1a/2b. ASICs are selectively permeable to Na^{+} but low amounts of other cations (Ca^{2+}, K^{+}, H^{+}, and Li^{+}) can also diffuse through ASICs. Pathophysiological events such as Inflammation, ischemia, hematoma, exercise etc. that cause the pH to fall below 7 and induce pain by stimulating nociceptive neurons are suggested to be regulated by ASICs [117]. However, the mechanism related to pain processing via ASICs is yet to be clarified. In addition to nociceptive functions, ASICs are also associated with other acute and chronic neurological diseases such as ischemic stroke, SCI, multiple sclerosis, HD, PD, migraine, glioblastoma, and epilepsy, and also with processes related to synaptic plasticity, learning, and memory [118–120]. Therefore, the study of modulators of ASICs has received much attention with regard to the treatment of such neurological diseases. Li et al. reported that agmatine might act as an extracellular non-proton ligand for ASIC3 [121]. They demonstrated that agmatine and its analog, arcaine, can activate both homomeric and heteromeric ASIC3 channels even in neutral pH conditions, and that the mechanism of activation is not via Ca^{2+} chelation but rather by non-proton ligand-sensitive domain interaction [117, 121].

Serotonin Receptors

Serotonin, also known 5-HT, is the one of the oldest neurotransmitters and receptors and is thought to have appeared approximately 700–800 million years ago in single cell eukaryotes [122]. The serotonin receptors are known to control emotional and psychological events in various natural conditions. In 1957, Gaddum and Picarelli proposed that the 5-HT receptors were of two kinds; "M" receptors, which were likely found in nervous tissue, and "D" receptors, which were likely found in muscle. However, based on the pharmacological properties, the modern classification divides 5-HT receptors into seven classes: 5-HT (1–7). All 5-HTs belong to the seven transmembrane domain-containing GPCR family with the exception of 5-HT3, which is a ligand-gated ion channel. To date, several subtypes of 5-HT1 (A, B, D–F), 5-HT2 (A–C), and 5-HT5 (A and B) have been identified [123]. Structurally, 5-HT receptors, as class A GPCRs, have seven transmembrane α-helices connected by large extracellular amino-termini and short intracellular carboxy-termini. They also have an intra-membrane helix (H8), which is connected via three extracellular/intracellular loops (EL/IL). The binding pocket, which is partially covered by EL2, is located in TM3, 5–7, and EL2 and EL3 [124, 125]. Most of the 5-HT receptors are found in the CNS and regulate animal and human behavioral responses e.g. anxiety, depression, locomotor activity, aggression, and other psychiatric conditions [126]. Agmatine does not exert any direct effect on serotonin or serotonin release in PC12 neurons [127]. However, the antidepressant effect of selective serotonin reuptake inhibitors is suggested to be associated with agmatine-induced imidazoline receptor modulation [74]. Zomkowski et al. demonstrated that agmatine exerts an anti-depressant-like function involving the 5-HT1A/1B and 5-HT2 receptors in mice, as assessed by the forced swim test [128]. The 5-HT3 receptors can be inhibited by agmatine, which is about $4 \pm 3\%$, lowest among all imidazoline drugs [129]. In a recent study, researchers found

that the antidepressant effect of agmatine was not mediated through serotonergic mechanism but via glutamatergic mechanism [130]. Agmatine was also reported to exert neuroprotective effects in response to corticosterone-mediated injury, via α2-adrenergic and 5-HT2A receptor-regulated Nrf2 induction [131]. However the mechanism of GPCRs blockage by agmatine are yet to discover (Fig. 3b).

Role of Agmatine in CNS Disorders

The neuroprotective effects of agmatine were first reported by Gilad in 1996 [132]. Since then, these effects have been demonstrated by numerous studies of neurological diseases [18, 26, 132–136]. In most studies agmatine has been administered via intravenous, intraperitoneal or oral route in different dosages (in vitro ranging 10 nM–100 μM and in vivo from 20–100 mg/kg). In the following section, we will discuss the role of agmatine in various CNS disorders.

Ischemic Stroke

Ischemic stroke, via occlusion of the cerebral artery(ies), results in energy depletion and subsequent death of cells in the vascular territory. This condition is a cause of long-term disability and ranks as the third most frequent cause of death following heart disease and cancer; yet, despite the high prevalence, the number of approved therapies remains low [137]. Agmatine has been effective in ameliorating neuropathological damage in in vivo and in vitro models of ischemic stroke. Previous studies have reported that agmatine led to a reduction in the size of ischemic infarctions or the loss of neurons under excitotoxic conditions in various stroke models in rodents [39, 41, 138]. Agmatine (100 μM) also improved the survival rate of neurons and astrocytes in vitro following ischemic and ischemia-like insults [139]. Additionally, Kim et al. reported that agmatine (100 mg/kg i.v.) mitigated the severe ischemia-induced neuronal damage in a cat model, which was used to mimic the clinical situation of hyperacute ischemic stroke [140], and in mice model agmatine (100 mg/kg, i.p.) was able to attenuate brain edema via regulation of aquaporin-1 expression in endothelial cells after experimental stroke [141]. Furthermore, agmatine treatment has been demonstrated to regulate neuroinflammation by decreasing the expression of proinflammatory factors such as nuclear factor kappa B (NF-κB) and matrix metalloproteinases in experimental stroke models [139, 142]. Therefore, the investigation of agmatine has clear clinical implication in terms of potential neuroprotective therapies for ischemic stroke and related conditions.

Traumatic Brain Injury (TBI) and Spinal Cord Injury (SCI)

TBI is a complex injury that occurs when an external force traumatically injures the brain. In the primary process, apoptotic cell death and brain edema occur immediately after the insult. After a period of hours to days, TBI leads to brain edema and hemorrhage, which trigger the inflammatory response. Following TBI, agmatine treatment decreased necrosis, blood–brain barrier disruption, and brain edema by reducing the phosphorylation of mitogen-activated protein kinases, the expression of aquaporins, and the promotion of NF-κB nuclear translocation [143]. Agmatine (50 mg/kg, i.p) was also able to improve the cortical lesion size, neurobehavioral outcome, and neuronal vitality, and reduce apoptosis, gliosis, increased hippocampal levels of glutamate, nitric oxide (NO), lactate-to pyruvate ratio, glycerol levels, and intracranial hypertension induced by TBI [20, 144]. Another condition associated with traumatic damage is spinal cord injury (SCI), which results in permanent disability or loss of movement and sensation below the site of injury, leading to paraplegia (thoracic level injury) or tetraplegia (cervical level injury). SCI causes neuronal and glial cell death, induces glial scar formation, and inhibits axonal regeneration and remyelination. Goracke-Postle et al. reported that agmatine was transported into spinal cord-derived nerve terminals in a concentration- and temperature-dependent manner [145]. Furthermore, agmatine (100 mg/kg, i.p.) administration was able to accelerate the recovery of neurological function and prevent the loss of motoneurons in an SCI rat model of spinal cord ischemia [133]. Park et al. demonstrated that transplantation of human mesenchymal stromal cells transfected with the ADC gene improved locomotor function and the viability of neurons and oligodendrocytes after SCI [146]. Following SCI, agmatine can promote remyelination, increase neuronal viability, and interrupt glial scar formation, which are related to increased bone morphogenetic protein (BMP) 2/7 expression in neurons, oligodendrocytes, and astrocytes. Furthermore, after complete spinal cord transection, agmatine can reduce collagen scar formation and enhance functional recovery associated with decreased tumor growth factor beta-2 and increased BMP-7 expression [19, 147].

Alzheimer's Disease (AD)

AD is a well-known degenerative brain disease characterized by the formation of amyloid-beta (Aβ)-containing plaques and intraneuronal deposits of neurofibrillary tangles [148]. It is the most common cause of dementia. Agmatine treatment improved the cognitive performance of rodents as assessed by the inhibitory avoidance task and the Morris water maze test [149, 150], and prevented morphine-induced memory

impairment in mice as assessed by the step-down inhibitory avoidance test [151]. In addition, agmatine pre-treatment reversed hippocampal extracellular-signal-regulated kinase and protein kinase B inactivation induced by scopolamine, suggesting that this endogenous substance may be a candidate treatment for amnesia [99, 152]. Our recent study demonstrated that agmatine (100 mg/kg i.p.) interrupted hippocampal Aβ accumulation, prevented cognitive decline as assessed by the Morris water maze, and attenuated apoptosis and expression of nuclear factor (erythroid derived 2)-like 2 (Nrf2)-mediated anti-oxidant signaling in a streptozotocin-induced AD rat model [153]. Agmatine (40 mg/kg i.p.) was also capable of protecting against Aβ25-35-induced neuronal toxicity and memory deficits as assessed by behavioral tests, such as the elevated plus maze, open field, memory version of the water maze task, and object recognition memory task [154]. In the mouse brain, agmatine suppressed the accumulation of Aβ and phosphorylated-tau, which may contribute to reduce the cognitive decline in mice subjected to high-fat diet [148].

Parkinson's Disease (PD)

Agmatine elicited neuroprotective effects in experimental models of PD, which is a chronic progressive disease characterized by the degeneration of dopaminergic neurons in the substantia nigra [155–157]. Daily agmatine treatment attenuated the dopaminergic neurotoxicity in the mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD [157]. A recent study reported that agmatine (30 mg/kg i.p.) repeatedly attenuated short-term memory and motor impairments induced by intranasal administration of MPTP in 15-month-old mice, which also causes a decrease in hippocampal glutamate uptake. In the human-derived dopaminergic neuroblastoma cell line (SHSY5Y), agmatine (10–500 nM) was capable of preventing cell damage caused by exposure to rotenone in a PD model [156]. It's beneficial effect could be associated with blocking of NF-κB nuclear translocation, suppression of ROS levels, and interruption of the apoptosis signaling cascade [155]. These results are associated with reducing oxidative damage and apoptotic cell death by agmatine in experimental models of PD.

Epilepsy

Epilepsy is a neurological disorder characterized by epileptic seizures, which increases with age. Indeed, agmatine appears to play an anti-epileptic role. It plays an anti-seizure role against maximal electroshock seizures (MES), an experimental model for generalized tonic–clonic seizures, in both mice and rats [158]. Agmatine (100 mg/kg i.p.) also improves the anticonvulsant function of phenobarbital and valproate in the MES model [159], and enhances the anticonvulsant effect of morphine or lithium chloride in mice via modulation of α2-adrenoceptors [160, 161]. In addition, agmatine mimicked the anticonvulsant effects of melatonin on the pentylenetetrazole (PTZ)-induced seizure threshold in mice [162], and had strong anticonvulsant effects in MES- and glutamate-induced seizure models in mice. These effects were likely related to *N*-methyl-D-aspartate receptor (NMDAR) antagonism [163]. In the hippocampi of PTZ-induced seizure model mice, a high dose of agmatine (20–80 mg/kg i.p.) reduced astrocytic hyperplasia and neuronal damage, indicating a reduction in the expression of the NR1 subunit of the NMDAR by agmatine [164]. This finding supports the involvement of the glutamatergic system in the anticonvulsant effects of agmatine. Based on these studies, agmatine is effective as an antiepileptic agent, and its effects are likely related to the L-arginine-NO pathway.

Other Neuropsychiatric Disorders

The therapeutic effects of agmatine also have been studied in different other neuropsychiatric disorders such as autism, schizophrenia, obsessive–compulsive disorder (OCD), depression and anxiety-like behaviours. Autism, also known as autism spectrum disorder (ASD), is a neurobehavioral condition lacks in social interaction and developmental impairment of language and communication skills with restricted/repetitive behaviors. The plasma agmatine levels in the ASD patients have been found to be remarkably lower than the non-ASD patients which suggests the involvement of agmatine to the ASD pathogenesis [165]. In the valproic acid animal model of autism agmatine ameliorated the ASD like symptoms by modulating the over-excitability of the neural circuit via inhibiting the over activation of the ERK1/2 signaling in the prefrontal cortex and hippocampus [166]. On the other hand, the plasma level of agmatine in the patients with schizophrenia found to be increased and in the rodent schizophrenia model agmatine, at a dose of (160 mg/kg i.p.), disrupted the paradigm of prepulse inhibition (PPI) of the acoustic startle reflex [167, 168]. Kotagale et al., suggested that agmatine alone can not induce schizophrenia like effects in rodents rather significant schizophrenic catalepsy can be found when agmatine (80 mg/kg i.p.) is injected into 5-HT1A receptor antagonist pretreated rodents [169]. However, agmatine was found to rescue the negative and cognitive schizophrenic symptoms but not the sensorimotor gating in MK-801-induced rat model of schizophrenia and pretreatment of a low dose of agmatine (20 mg/kg i.p.) could rescue the psychotomimetic drug phencyclidine (PCP) induced PPI deficit [170]. In the OCD rodents agmatine can effectively reduces the compulsive like behaviours which might be related to NO in brain [171, 172]. The agmatine level in the postmortem brain of the individuals with/without major

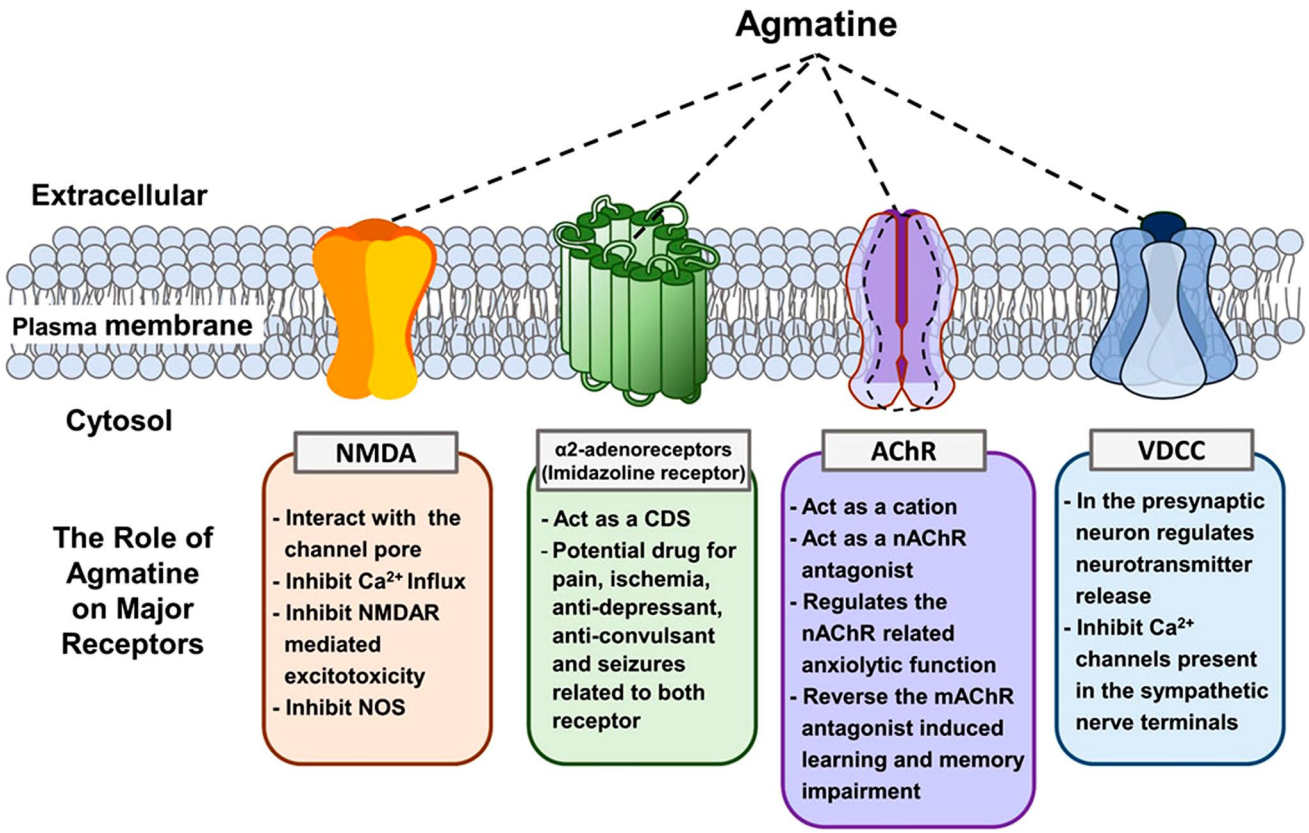

Fig. 4 Agmatine: role on different ion channel and receptors. Agmatine can regulate the function of different receptors or ion channels by binding to them or blocking them, which modulate normal cellular functions and disease progression

depressive disorder (MDD) and suicide found to be lower than the normal individuals [173]. In the stress induced and CREB-regulated transcription coactivator 1 (CRTC1) knockout rodent models of depression agmatine showed marked anti-depressive and anti-anxiolytic effects through oxidative homeostasis pathway which may also involve serum CORT and BDNF levels [131, 174, 175].

Conclusion

The presence of agmatine in mammals was first noted in 1994 after its initial discovery by Nobel Laureate Albrecht Kossel in 1910. In mammals, it was identified as a CDS while searching for the endogenous ligand for I-1. A wide range of studies have since been performed and have shown that agmatine possesses most of the characteristics of an endogenous neurotransmitter and can bind to a variety of receptors or ion channels and modulate their functions (Fig. 4). Previous studies showed that, by modulating receptors or ion channels, agmatine exerted protective effects in many chronic and acute neurological diseases such as ischemic stroke, traumatic injury, AD, PD, schizophrenia, anxiety, depression, autism, and addiction. In addition to neuroprotection against neurological diseases, agmatine has been reported to function as an anti-diabetic, anti-hypertensive, nephron-protective, and gastro-protective drug. Our review provides a brief summary of the diseases related to the nervous system, and receptors and ion channels acted upon by this primary amine. This review will provide the basic information to the researchers studying the functional mechanism of agmatine on those receptors and ion channels which are not clearly understood yet. However, to perfect the use of agmatine as a choice pharmacological agent, a wide range of future studies are needed in order to determine its ligand binding and functional mechanisms related to the receptors and ion channels.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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