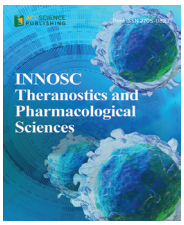
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REVIEW ARTICLE

Agmatine as a Novel Treatment Option for Neuropathies: Experimental Evidences

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Abstract:

N-methyl-D-aspartate receptor (NMDAR) antagonist, a subclass of glutamate receptors or nitric oxide synthase (NOS) inhibitors, prevents neuronal plasticity. However, neural plasticity plays a major role in the pain caused by inflammation and neuropathy, providing clinical opportunities for the use of NOS inhibitors and NMDAR antagonists in the treatment of chronic pain. The neuromodulator agmatine has both NOS inhibitory and NMDAR antagonistic activity, and it controls a range of neurotransmitters and signaling pathways in the brain and spinal cord. The effects of agmatine on pain modulation are described and explored in this article, along with a potential mechanism of action for these effects. We specifically offer evidence to support further clinical and pre-clinical trials looking into agmatine as a novel therapeutic agent for neuropathic pain.

Keywords: Agmatine, Neuropathic pain, Nitric Oxide, N-methyl-D-aspartate

1. Introduction

Allodynia and hyperalgesia are a part of neuropathic pain (NP), a type of chronic pain brought on by a lesion or illness that affects the somatosensory system in the peripheral or central nervous system (CNS) [1]. Damage to the peripheral nervous system (PNS) caused by infections, some medicines, metabolic illnesses, and mechanical trauma are the main causes of NP. Numerous mechanisms, including alterations in gene expression and adjustments to ion channels that result in ectopic activity in the PNS, are thought to contribute to NP. In the CNS, numerous gene controls may also be changed. There is an alteration in afferent inputs of both nociceptive and non-nociceptive pathways due to neuronal death and excessive synaptic activity [2]. Research on animal models of peripheral nerve injury suggests that N-methyl-D-aspartate (NMDA) receptors (NMDARs) have a function in NP [3]. According to some studies, treatment of NMDAR antagonists eliminates the impulsive pain and the thermal and mechanical hyperalgesia induced in rats with loose sciatic nerve ligation. The study also implies that inhibiting NMDAR delays pain-related behavior after nerve injury [4]. It has been demonstrated that activation of NMDAR in different parts of the CNS causes nitric oxide generation, which, in turn, causes a Ca^{2+}-dependent rise in cyclic guanosine monophosphate (cGMP). The NMDAR is activated, which increases intracellular Ca^{2+} and

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triggers nitric oxide synthase (NOS) to generate nitric oxide from free L-arginine. In this process, nitrate and nitrite are stable metabolites of nitric oxide, and monitoring their concentrations is an excellent way to assess the homeostasis of nitric oxide [5]. According to immunohistochemistry research, NOS-positive cells have been discovered in several regions of the animal and human brains, including the cerebellum and brainstem [6]. Studies suggest that sympathetic blockade caused by surgical and chemical agents reversibly reduces NP symptoms and that sympathetic efferent activity plays a significant permissive role in the emergence of hyperalgesia and allodynia in humans and animals suffering from NP [7].

Agmatine is an endogenous neurotransmitter that is produced in the mammalian brain and other tissues. It is the decarboxylated form of L-arginine and an NMDAR antagonist. It is an inhibitor of NOS, and it binds to α2-adrenoceptors, imidazoline (I1/I2) receptors, and serotonin (5-hydroxytryptamine or 5-HT) receptors with lesser affinity than NMDAR [8-10] (Figure 1). Studies have reported that agmatine is effective at reducing hyperalgesia and/or allodynia in a variety of chronic NP models when administered spinally and systemically. Agmatine also significantly reduces inflammation-related pain in animal models [11-13]. Agmatine has been shown to improve opioid analgesia and lessen diabetic neuropathy in rats, despite the fact that it does not appear to be an effective analgesic for acute phasic pain. According to a recent clinical investigation, agmatine is effective and safe for relieving pain and enhancing the quality of life in individuals with lumbar disk-associated radiculopathy. Pyramidal cells in the rat hippocampus and other parts of the brain contain agmatine [14]. Numerous physiological, pharmaceutical, and behavioral research suggests that hippocampus formation is crucial for the effective and motivating aspects of pain perception. The role of agmatine in the primary sense of pain has been reported [15,16]. After a peripheral nerve lesion, the proinflammatory cytokine tumor necrosis factor-alpha (TNFα) was markedly elevated in the hippocampus, and its administration into the hippocampus led to NP-like symptoms [17,18]. In this review, the studies indicating how agmatine affects NP are examined along with the underlying mechanisms of action. We also provide data to support clinical trials that would demonstrate agmatine's effectiveness as an NP adjuvant or monotherapy.

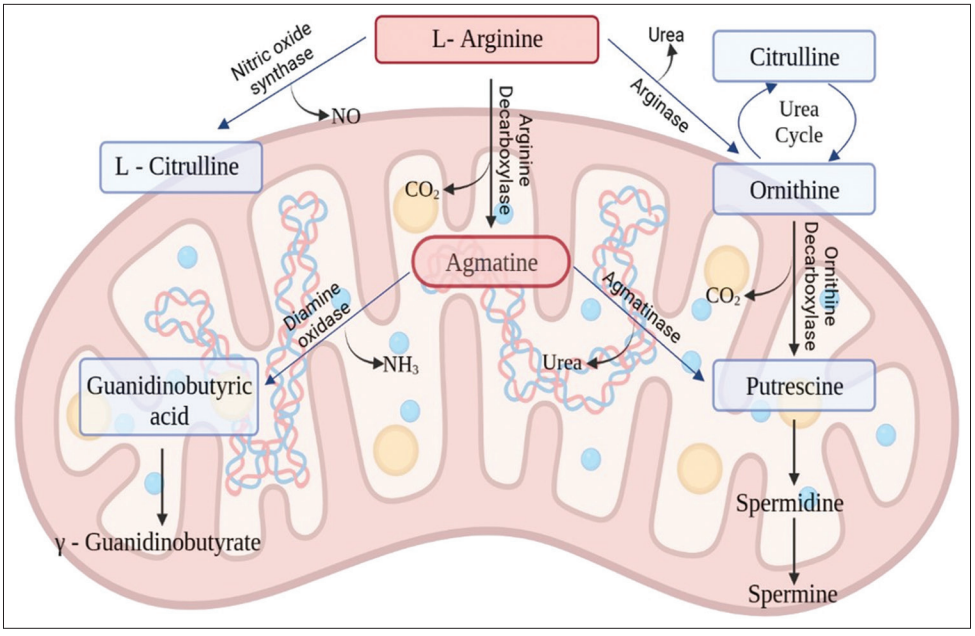


Figure 1. Schematic representation of biosynthesis and metabolism of agmatine inside the mitochondria of astrocytes. L-arginine acts as precursor molecule, which on decarboxylation by the enzyme arginine decarboxylase, coverts to agmatine. Agmatine is then metabolized to guanidinobutyric acid by the enzyme diamine oxidase.

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2. Etiology

NP is associated with various medical conditions, the causes of which vary considerably. Metabolic (hypothyroidism), compressive (carpal tunnel syndrome), infectious (huma immunodeficiency virus, HIV), toxic (alcohol), traumatic (spinal cord injury), and ischemic (diabetes) processes are all causal factors of NP [19]. Multiple NP mechanisms may be linked to a single medical issue. In postherpetic neuralgia, viral, inflammatory, and ischemic processes have been discovered. Understanding the fundamental causes of NP may lead to advancements in classification, diagnosis, and treatment [20].

3. Classification of NP

Pain can be classified into neuropathic (pain caused by damage to the nervous system) and nociceptive (pain caused by stimulation of peripheral nociceptors in the skin, joints, and muscles). The primary distinction between NP and nociceptive is that NP is characterized by a lack of constant nociceptive input. Peripheral and central NP is the two categories into which NP is categorized [21]. A lesion or dysfunction causes peripheral NP in the PNS, such as postherpetic neuralgia, diabetic neuropathy, or causalgia. Thalamic pain, post-stroke pain, and post-spinal cord injury pain are examples of central NP that are linked to CNS damage or dysfunction. In addition, NP can either be induced by or unaltered by stimuli. Hyperalgesia and allodynia brought on by mechanical, thermal, or chemical stimulation are what set stimulus-evoked pain apart. Chronic or episodic, stimulus-independent (spontaneous) pain is usually described as shooting, burning, or stabbing [22].

4. Pathophysiology

There is currently no conclusive pathophysiology for NP. It is impossible to predict the underlying mechanisms based on a patient's etiology of the neuropathy, pain distribution, or symptoms. There are several hypothesized mechanisms of NP. NP can develop when there is injury or pathological damage to the PNS or CNS [23]. To summarize **(Figure 2)**, the understanding of NP, increased peripheral nerve firing, decreased CNS inhibition, and altered CNS processes result in pain amplification and propagation.

5. Pharmacological treatment for the management of NP

The management of NP is quite challenging. Despite taking the recommended medications for their diseases, patients with NP will still generally suffer from moderate to severe pain [23,24]. Therefore, recommendations for the pharmaceutical therapy of NP must be supported by data. Numerous drugs have consistently demonstrated efficacy in meta-analyses and randomized controlled clinical studies, including antidepressants with serotonin reuptake and norepinephrine inhibitors, Ca^{2+} channel α2-δ2-ligands, opioid analgesics, and topical analgesics such as lidocaine [25]. The mode of action, information on dosage, and side effects for different medication classes are summarized in **Table 1**.

6. Preclinical animal models of NP

The high degree of variability in the etiology of NP, which can be caused by conditions like diabetes mellitus or anti-cancer chemotherapy, as well as brain lesions, demyelinating diseases of the spinal cord, and peripheral neuropathy, is a major concern for research into and treatment of this condition [32]. Although the case histories of most NP patients do not resemble those of preclinical studies, they do allow for the investigation of disease processes, and many clinically used treatments can reverse the pain behaviors seen in these models [33]. The majority of preclinical studies are carried out on rodents and involve direct nerve injury to the sciatic nerve. Animal models that mimic the etiology of human diseases, such as diabetic neuropathy and some chemotherapy medications, are available in addition to surgical models [34,35]. However, due to inefficiency or adverse effects, it has long been difficult to effectively translate painkillers from animal models to clinical studies [36,37]. Due to the highly variable etiology of NP in humans compared to the relatively constrained animal models, the inbred (and thus genetically homogeneous) animal subjects in comparison to the more genetically diverse human population, and the difference in how pain is assessed (i.e., most animal studies measure

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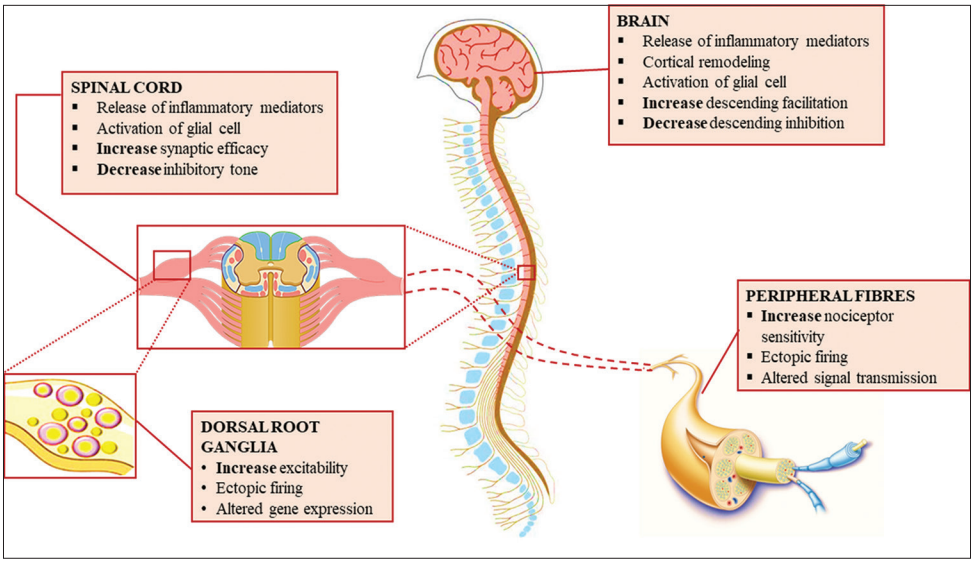


Figure 2. Diagrammatic representation of neuropathic pain pathophysiology in the brain and spinal cord.

stimulus-evoked withdrawal behaviors, whereas NP patients frequently describe spontaneous pain), among other differences. Animal models of NP have their limitations, and translation is far from perfect at this time, but these models have shown that NP involves changes at all levels of the pain pathway, from variations in the expression of the sensory neuron protein to changes in spinal cord synaptic function and the brain's descending control of pain [25,37]. Some of the studied animal models of NP are described in **Table 2**.

7. Agmatine as a potential treatment for NP

Dysesthesia or pain that results from stimuli that are generally non-painful (allodynia) are two characteristics of NP, which is caused by injury to or disease of the somatosensory nervous system [53,54]. Agmatine has been demonstrated to lessen pain-related behaviors in rodent models of neuropathic sensory hypersensitivity [55,56]. In contrast to morphine-based analgesics, this action is mediated by NMDAR regulation and nitric oxide signaling. Concerning the latter, it has been demonstrated that agmatine increases the analgesic efficacy of morphine through the α2-adrenoceptor-mediated mechanism [8,57,58]. It has been demonstrated that agmatine inhibits the production of advanced glycation end-products and enhances nerve regeneration in diabetic neuropathy [59]. A placebo-controlled clinical experiment showed that agmatine treatment might be efficient in humans as well. Agmatine produced anti-allodynic and anti-hyperalgesic benefits in animal models of chronic neuropathic and inflammatory pain [14]. Acute delta opioid receptor-mediated analgesia was potentiated and enhanced in response to intrathecal agmatine administration. Chronic pain is a typical side effect of traumatic nerve injury, which can also activate NOS, NMDA, and other common pathogenic cascades. NOS produces nitric oxide from L-arginine when NMDAR activation results in an increase in intracellular Ca^{2+}. It is generally known that NMDAR is crucial in the processing of chronic pain brought on by injury to peripheral nerves. A decrease in nitric oxide levels and noradrenergic activity in the brain may have contributed to agmatine's attenuation of the sciatic nerve ligation-induced NP model. These beneficial effects of agmatine may be attributed to the engagement of noradrenergic neurons in the locus coeruleus, which are implicated in the development and/or maintenance of allodynia and hyperalgesia in the context of peripheral nerve injury. Agmatine has the ability to bind to both the α2-adrenergic and imidazoline receptors [60]. One hypothesis was that an imbalance of supraspinal facilitation and inhibition constituted the root of neuropathic hypersensitivity. The locus coeruleus may be involved in the bidirectional control of pain [31]. Lesions in the noradrenergic locus coeruleus were shown to suppress the onset of allodynia and hyperalgesia, while noradrenergic reuptake inhibitors were found to reduce NP. Even though it

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Table 1. First-line treatment for patients with neuropathic pain

Mechanism of action		Dose (starting/ maximum)	Side effects
Selective serotonin-norepinephrine reuptake inhibitors (SSNRIs)			
Venlafaxine [26]	Inhibits both norepinephrine and 5-HT reuptake	37.5 mg (once or twice daily)/225 mg (daily)	Nausea
Duloxetine [27]	Inhibits both norepinephrine and 5-HT reuptake	30 mg (once daily)/60 mg (twice daily)	Nausea
Tricyclic antidepressants (TCAs) [28]			
Desipramine Nortriptyline	Inhibits the reuptake of norepinephrine and/or 5-HT, blocks Na^+channels, anticholinergics	25 mg (bedtime)/150 mg (daily)	Anticholinergic effects (dryness of mouth, weight gain, urinary retention, sedation)
Topical lidocaine [29]			
5% lidocaine patch	Blockade of Na^+channels	1–3 patches/3 patches	Rash, local erythema
Calcium channel α2-δ ligands [30]			
Pregabalin	Decreases release of norepinephrine, glutamate, and substance P, with ligands on the α2-δ subunit of voltage-gated calcium channel	50 mg (thrice daily or 75 mg twice daily)/200 mg (thrice daily) or 300 mg (twice daily)	Sedation, peripheral edema, dizziness
Gabapentin	Decreases release of norepinephrine, glutamate and substance P, with ligands on the α2-δ subunit of voltage-gated calcium channel	100–300 mg (once to thrice daily)/1200 mg (thrice daily)	Sedation, peripheral edema, dizziness
Opioid agonists [31]			
Tramadol	Agonist of μ-receptor inhibits the reuptake of norepinephrine and serotonin	50 mg (once or twice daily)/400 mg (daily as a long-acting drug)	Vomiting/nausea, constipation, dizziness
Morphine, oxycodone, methadone, levorphanol	μ-receptor agonist (oxycodone also causes κ-receptor antagonism)	10–15 mg morphine every 4 h or as needed (equianalgesic doses should be used for other opioids)/no maximum doses	Vomiting/nausea, constipation, dizziness

5-HT: 5-hydroxytryptamine (serotonin)

seems like the locus coeruleus which is a structure that prevents pain, some studies indicate that it may actually have a function in NP facilitation. There has been speculation that the coeruleospinal noradrenergic fibers are involved in the descending inhibition of spinal pain transmission.

Agmatine has been demonstrated to lower 3-methoxy-4-hydroxyphenyl ethylene glycol (MHPG) and norepinephrine levels in the brainstem while increasing the norepinephrine (NP) pain threshold. It was suggested that the reduction of NP was due to agmatine's activation of presynaptic α2-adrenoceptors, which reduced central noradrenergic activity. The oxidative and nitrosative stress elicited by persistent hyperglycemia in diabetes mellitus is regarded as one of the key factors in the disease's related brain dysfunction. Increased oxidative stress promotes vascular dysfunction and endoneurial hypoxia, which impairs the function of the motor and sensory nerves. In addition, rats with diabetes caused by streptozotocin were also found to have an L-arginine shortage. Nitric oxide, agmatine [61], and glutamate all have similar effects on the CNS through

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Table 2. Animal models of neuropathic pain

No.	Name of animal model	Principle	Species
1.	Axotomy (complete sciatic nerve transection) [33,38]	Whole transection of sciatic nerve	Rats
2.	Acrylamide-induced injury [39]	Prolonged administration of acrylamide	Rats
3.	Chronic constriction injury [33,40]	Four loose ligatures around the sciatic nerve	Rats, mice
4.	Partial sciatic nerve ligation (Seltzer Model) [41,42]	Tight ligation of one-third to half of the sciatic nerve	Rats, mice
5.	Orofacial pain [43]	Injection of formalin, carrageenan into temporomandibular joints and maxilla	Rats, mice
6.	Spinal nerve ligation [44,45]	Tight ligation of L5 and L6 spinal nerves	Rats
7.	Spared nerve injury [46,47]	Axotomy of tibial and common peroneal nerves	Rats, mice
8.	Trigeminal neuralgia [48,49]	Compression of trigeminal ganglion; chronic constriction injury to the infra-orbital nerve	Rats Rats
9.	Diabetes-induced neuropathy (streptozotocin-induced andgenetic models) [50,51]	Persistent hyperglycemia-induced changes in the nerves	Rats, mice
10.	Weight drop or contusive spinal cord injury [52]	Dropping a weight over the exposed spinal cord	Rats, mice

NMDAR [61]. Agmatine likely works on spinal imidazoline receptors to reduce pain [14]. Agmatine was reported to have lessened the antiallodynic and anti-hyperalgesic effects in diabetic NP when combined with an imidazoline receptor antagonist. In spinal nerve ligation animal modelswith diabetic NP, agmatine also exerts an antiallodynic effect. When all underlying causes of NP are taken into account, agmatine can substantially treat numerous neuropathies owing to its NMDAR antagonist, NOS inhibitory, and anti-inflammatory effects. One of the pathogenic pathways that can be triggered by neuronal injury and chronic pain is the activation of NMDAR and NOS [62]. All isoforms of NOS, especially the most powerful types, as well as NMDAR and NMDA-mediated Ca^{2+} currents, have all been reported to be blocked by agmatine **(Figure 3).**

It has recently been reported that cisplatin-induced mechanical allodynia, sciatic nerve degeneration [63,64], and dorsal root ganglia cell senescence may be prevented by agmatine. Studies indicate that agmatine's neuroprotective and antiallodynic effects were not significantly increased by L-NAME. Another study demonstrated that NOS inhibitors and NMDAR antagonists [65] can activate tryptophan hydroxylase to enhance the release of 5-HT. Furthermore, it was suggested that the production of neurotrophic chemicals by macrophages, activated microglia, and infiltrating monocytes contribute significantly to neuroinflammation. These compounds have both pro-inflammatory and neuroprotective effects. It was suggested that agmatine could enhance the anti-inflammatory M2 macrophage properties without boosting cell numbers. Its anti-neuropathy effectiveness may possibly be due to the proinflammatory M1 and anti-inflammatory M2 macrophages' induction of the activation of axonal regeneration after neuronal damage. The hippocampus is one of the many regions of the brain where agmatine is widely distributed and colocalizes with sigma receptors. Sigma receptors were present in sciatic nerves [66,67] as well, and Sigma-1 receptors, in particular, were crucial for controlling NP. Furthermore, some data suggest that NP may have higher-than-normal hippocampal TNFα levels [68]. Sigma-1 and Sigma-2 receptor [63] agonists were shown to boost TNFα production, whereas agmatine lowered TNFα levels, indicating that inhibiting these receptors in NP-induced rats may be beneficial. As a result, the antinociception induced by agmatine may include the serotonergic,

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opioidergic [69-72], imidazoline [11,73,74], α2-adrenergic [75,76], and opioidergic sigma receptors, which have been recently shown to have a substantial role in the antinociceptive effect of agmatine on NP. Hence, additional research is required on these predictions **(Table 3).**

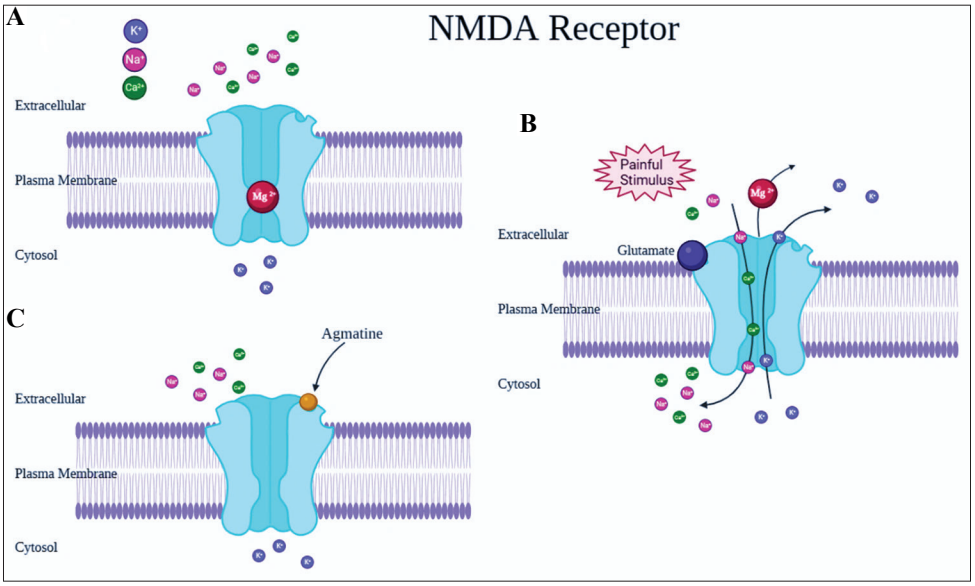


Figure 3. Effect of agmatine on N-methyl-D-aspartate (NMDA) receptor. (A) At the resting stage, NMDA receptor is blocked by magnesium ion. (B) During painful stimulus, there is release of an excessive amount of glutamate ions, which over-activate the receptor and transport the ions in and out, leading to Ca^{2+} excitotoxicity. (C) Agmatine, an NMDA receptor antagonist, binds to the receptor and attenuates the Ca^{2+} ions excitotoxicity.

Table 3. Experimental evidence for the analgesic effect of agmatine on different animal models of neuropathic pain

Behavioral test	Neuropathic pain induction	Route of administration	Dose	Effect
Von Frey test [77]	Spinal nerve ligation	i.t.	0.3 nmol	+
Von Frey test [77]	i.t. Dynorphin	i.t.	0.3 nmol	+
Cold hyperalgesia [78]	Sciatic nerve ligation	i.p.	10 – 100 mg/kg	+
Thermal hyperalgesia [7]	Sciatic nerve ligation	i.p.	30 – 400 mg/kg	+
Von Frey test [79]	Spinal nerve ligation	i.p.	10 – 100 mg/kg	+
Von Frey Test [79]	Diabetic neuropathy	i.p.	10 – 100 mg/kg	+
Plantar test [10]	Diabetic neuropathy	i.t.	4.4 – 438 nmol	+
Von Frey test [10]	Diabetic neuropathy	i.t.	4.4 – 438 nmol	+
Paw pressure test [10]	Diabetic neuropathy	i.t.	4.4 – 438 nmol	+
Cold hypernociception [80]	Partial sciatic nerve ligation	i.p.	30 mg/kg	+
Thermal hypernociception [54]	Partial sciatic nerve ligation	i.p.	30 mg/kg	+
Cold allodynia Thermal allodynia Mechanical allodynia [12]	Partial sciatic nerve ligation	i.h.	2.5 – 10 µg/side/rat	+
Cold allodynia Thermal allodynia Mechanical allodynia [12]	Partial sciatic nerve ligation	i.p.	40 – 120 mg/kg	+

i.h: Intrahippocampal; i.p: Intraperitoneal; i.t.: Intrathecal; +: Analgesic effect.

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8. Conclusions

Multiple, intricate mechanisms lead to the emergence of NP. Animal models were used to better define the therapy objectives and to comprehend the pathophysiological mechanisms. Given that agmatine has numerous targets that are likewise implicated in NP and open up novel therapeutic possibilities, there have been numerous scientific studies on the impact of agmatine on NP. Agmatine has a high safety profile and has not been demonstrated to negatively affect behavior, locomotion, or cardiovascular systems in naive animals. According to experimental investigations, agmatine has shown considerable potential for the development of effective treatment for this illness.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Mayur Kale
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Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

Not applicable.

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