

# Cannabinoids and agmatine as potential therapeutic alternatives for cisplatin-induced peripheral neuropathy

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**Abstract:** Cisplatin is a widely used antineoplastic agent in the treatment of various cancers. Peripheral neuropathy is a well-known side effect of cisplatin and has the potential to result in limiting and/or reducing the dose, decreasing the quality of life. Unfortunately, the mechanism for cisplatin-induced neuropathy has not been completely elucidated. Currently, available treatments for neuropathic pain (NP) are mostly symptomatic, insufficient and are often linked with several detrimental side effects; thus, effective treatments are needed. Cannabinoids and agmatine are endogenous modulators that are implicated in painful states. This review explains the cisplatin-induced neuropathy and antinociceptive effects of cannabinoids and agmatine in animal models of NP and their putative therapeutic potential in cisplatin-induced neuropathy.

**Keywords:** agmatine, anandamide, cisplatin, neuropathy

## Introduction

Cisplatin (*cis*-dichlorodiammineplatinum II) is the first agent of platinum drugs that is widely used as a first-line treatment for several solid and blood cancers.<sup>1</sup> Platinum derivatives exert antitumor activity by reacting with the DNA, and they damage DNA by intra- and interstrand crosslinks, which then induce apoptotic cell death in dividing cells and cancer cells.<sup>2</sup> They hardly cross the blood–brain barrier but have a high affinity to the peripheral nervous system.<sup>3</sup> Despite its efficacy, cisplatin causes predominantly sensory axonal peripheral neuropathy (PN), which limits the dose delivered, reduces likelihood of an effective treatment and affects patients' quality of life.<sup>4</sup> The major symptoms of this condition are sensory loss, painful paresthesias, weakness, tremors, numbness, temperature sensitivity and hyperalgesia in a “stocking and glove” distribution.<sup>5</sup> The symptoms may begin after the first dose or at the end of the therapy and may appear after weeks to several months even after the discontinuation of therapy, a process known as coasting phenomenon.<sup>4</sup> Higher cumulative doses and long-lasting cisplatin treatment may also lead to chronic and irreversible PN.<sup>6</sup> Approximately 60% of patients receiving a total cumulative cisplatin dose ranging from 225 to 500 mg/m<sup>2</sup> suffer from peripheral nerve damage,<sup>7</sup> and 10% of them experience treatment-emergent grade 3/4 neurotoxicity.<sup>8,9</sup> The exact mechanism of cisplatin-induced PN has not been fully elucidated; however, various underlying mechanisms have been proposed.

Neuropathic pain (NP) is a chronic pain arising as a direct consequence of a lesion or disease affecting the somatosensory system in either the periphery or centrally.<sup>10</sup> PN results from some type of damage to the peripheral nervous system caused by mechanical trauma, metabolic diseases, certain drugs and infections.<sup>11</sup> Several mechanisms

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are thought to be responsible for NP, some of which consist of altered gene expression and changes in ion channels that cause ectopic activity in the peripheral nervous system. In addition, many gene regulations may also be changed in the central nervous system. Neuronal death and excessive synaptic interactivity lead to changes in both nociceptive and innocuous afferent inputs.<sup>11</sup>

Cisplatin has been found at higher levels in dorsal root ganglia (DRG) than in peripheral nerve or in the central nervous system in patients with cisplatin therapy.<sup>12,13</sup> The severity of PN correlates with platinum levels in these cells.<sup>6,14</sup> The presence of an abundant fenestrated capillary network and absence of an effective blood–brain barrier in the DRG<sup>15</sup> allow platinum drugs to accumulate in the DRG with easy access to sensory neurons, explaining the main sensory symptoms in PN.<sup>16</sup>

Cisplatin could also affect the central nervous system and extensively cause cytotoxicity when injected directly into the brain.<sup>17</sup> Cytoplasmic changes including deep invaginations between satellite cells and the neuronal surface and formations of vacuoli in satellite cells of DRG were also reported by cisplatin treatment.<sup>18</sup> There are some limited evidence that cisplatin affects proinflammatory cytokine expression and causes some changes in immune signaling pathways. However, the results of these neuroinflammatory responses need to be clarified by further investigations.<sup>19</sup> Copper transporter 1 and copper-transporting ATPases, expressed on the DRG membrane, are responsible for cellular uptake and accumulation of cisplatin in sensory neurons and contribute to the development of PN.<sup>20</sup> After cisplatin enters into the cell, it directly binds to DNA and forms interstrand crosslinks and intrastrand adducts by changing the tertiary structure of DNA.<sup>20,21</sup> Then, cell cycle kinetics is disrupted within the DRG, and these cells reenter into the cell cycle that results with apoptosis.<sup>22</sup> The latter mechanism involves oxidative stress and mitochondrial dysfunction as a component of neuronal apoptosis.<sup>23</sup> Cisplatin binds to mitochondrial DNA (mtDNA) and nuclear (n) DNA in the DRG.<sup>24</sup> mtDNA does not have any DNA repair system; thus, platinum adducts cannot be removed from mtDNA. This causes perturbations in protein synthesis and mitochondrial respiratory chain reactions.<sup>24</sup> Mitochondrial dysfunction and failure in energy metabolism of the cell lead to overproduction of reactive oxygen species and induce cellular oxidative stress. Moreover, cisplatin causes mitochondrial release of cytochrome c and caspases promoting apoptosis via the mitochondrial intrinsic pathway.<sup>23</sup> Cisplatin also increases the activity of p53 and p38 proteins and extracellular signal-regulated kinase

(ERK) 1/2 signaling pathways.<sup>25</sup> In addition, it may increase the expression levels of transient receptor potential vanilloid 1 (TRPV1), transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential melastatin 8 (TRPM8) in cultured DRG cells.<sup>26,27</sup>

Many agents have been proposed to manage chemotherapy-induced NP such as vitamin E, glutamine,  $\alpha$ -lipoic acid, glutathione, calcium–magnesium, acetyl cysteine, acetyl-L-carnitine, amifostine, diethyldithiocarbamate and glutathione. However, none of these agents has been proven effective.<sup>28</sup> Some agents such as caffeic acid phenethyl ester,<sup>29</sup> pifithrin- $\mu$ ,<sup>30</sup> APX2009,<sup>31</sup> mesenchymal stem cells,<sup>32</sup> Org 2766, glutathione, amifostine and various neurotrophic growth factors<sup>28</sup> were suggested to prevent or limit the cisplatin neurotoxicity, which are still under investigation. Therefore, there is still a great need for effective treatments.

In this review, the studies demonstrating the antinociceptive effects of endogenous modulators cannabinoids and agmatine in animal models of NP, as well as the mechanisms of action related to such effects, are discussed. We present the evidence to support the potential of cannabinoids and agmatine as adjuvants/monotherapy for cisplatin-induced PN.

## Cannabinoids and NP

Cannabinoids represent a wide range of endogenous or exogenous compounds that include phytocannabinoids, the natural compounds found in plants of the genus *Cannabis*; endogenous cannabinoids and synthetic ligands.<sup>33</sup> *Cannabis* has an ancient medicinal history, but the potential value of the cannabinoids for medicinal purposes arose from the discovery of cannabinoid receptors and their endogenous ligands.<sup>33–35</sup> Investigations into the chemistry of *Cannabis* began in the mid-19th century, and cannabinol, cannabidiol (CBD) and the main active compound delta-9-tetrahydrocannabinol ( $\Delta$ -9-THC) were isolated, respectively.<sup>33,36</sup> Another cornerstone in cannabinoid research was the identification of cannabinoid receptor system between 1980 and 2000s, and then, this system was named as endocannabinoid system.<sup>36</sup>

There has been an increasing interest in the therapeutic potential of cannabinoids for the treatment of many disorders and symptoms.<sup>35</sup> However, cognitive–behavioral effects and widely illicit use of cannabinoids in the world have created political and regulatory obstacles, and they were included as controlled drugs in the United Nations Single Convention on Narcotic Drugs, and their use is illegal in most countries.<sup>37</sup>

Cannabinoids produce their actions through the activation of G-protein-coupled cannabinoid receptors, CB1 and CB2.<sup>32,36</sup> Activation of both CB1 and CB2 receptors inhibits

adenylate cyclase activity, and CB1 receptor activation can also inhibit type 5-HT<sub>3</sub> ion channels; modulate the production of nitric oxide (NO); alter conductance of calcium, potassium or sodium channel and activate the Na<sup>+</sup>/H<sup>+</sup> exchanger, the pathways that have been implicated in pain transduction and perception.<sup>32,38,39</sup> CB1 receptors are found mainly in the central nervous system, and CB2 receptors are primarily localized to cells of the immune system.<sup>32</sup> More significantly for the purposes of the present review, CB1 receptors are those present in sensory neurons (DRG and trigeminal ganglia), as well as defense cells such as macrophages, mast cells and keratinocytes.<sup>40</sup> Few CB2 receptors are located in the brain, spinal cord and DRG, but they increase in response to peripheral nerve damage. They modulate central neuroimmune interactions and interfere with inflammatory hyperalgesia.<sup>41</sup>

Anandamide (*N*-arachidonylethanolamine [AEA]) and 2-arachidonoylglycerol (2-AG) are the main endogenous ligands of cannabinoid receptors derived from the membrane-localized phospholipid precursors and are recruited during tissue injury to provide a first response to nociceptive signals.<sup>34,42</sup> Besides cannabinoid receptors, they have been also shown to exert several effects via other targets, such as transient receptor potential (TRP) channels; orphan G-coupled receptors such as GPR55, GPR92, GPR18 and GPR119; T-type calcium channels; glycine receptors and GABA<sub>A</sub> receptor.<sup>38</sup>

AEA is synthesized from the phosphatidylethanolamine, an abundant lipid present in the cell membrane, by *N*-acyltransferase and phospholipase D, and it is mainly degraded by fatty acid amide hydrolase (FAAH).<sup>43</sup> 2-AG is synthesized from diacylglycerol by diacylglycerol lipase and is primarily metabolized by monoacylglycerol lipase (MGL).<sup>43</sup>

## Antinociceptive effects of cannabinoids in animal models of NP

Studies evaluating the presence of hyperalgesia following blockade of CB1 receptors provided early physiological support for the hypothesis that endocannabinoids suppress pain.<sup>39</sup> Since then many studies have been performed to investigate the antinociceptive effects of cannabinoids and their modulation in acute, inflammatory and NP models. The discovery of endocannabinoid system, as one of the neuromodulatory system involved in the pathophysiology of NP, raised the interest for the development of new therapeutic strategies.<sup>32,44,45</sup> Endocannabinoid system is expressed highly in neurons and immune cells that are crucial for the development of NP,<sup>46–48</sup> and there is also evidence available stating that endocannabinoid levels are altered in several regions of ascending and descending pain pathways in NP states.<sup>49</sup> Furthermore, endocannabinoids have been shown to interact with other receptor systems, including GABA, serotonin, adrenergic and opioid receptors, which are involved in the antinociceptive effects of common NP medications.<sup>32,38,45,50</sup> Based on the existing data, new pharmacological agents have been investigated in various animal models of NP through the manipulation of cannabinoid receptors and transporters or blocking enzymes involved in the endocannabinoid degradation (Table 1).<sup>32,38,44,45</sup>

Cannabinoid receptor agonists have shown antinociceptive properties in a variety of NP models. They have been shown to alleviate hyperalgesia in peripheral nerve injury-induced,<sup>51–60</sup> chemotherapy-induced,<sup>61–68</sup> diabetes-induced<sup>69–74</sup> and antiretroviral-induced<sup>75</sup> neuropathy models. The anti-hyperalgesic effect of cannabinoids was suggested to be

**Table 1** Substances modulating the endocannabinoid system in NP

Group of substances	Samples
Endocannabinoids	AEA (Anandamide), <i>N</i> -oleoylethanolamide, <i>N</i> -palmitoylethanolamide, <i>N</i> -arachidonoyl dopamine, 2-arachidonoylglycerol
Phytocannabinoids and synthetic analogs	9-THC, CBD, β-caryophyllene, Cannador, cannabis, eCBD, nabilone, nabilisol, Nabiximols, Marinol (dronabinol), CB13, levonantradol, nabilone
CB1 agonists	ACEA, HU-210, Met-F-AEA
CB2 agonists	A-796260, A-836339, AM1241, AM1710, AM1714, Compound 27, GW405833, JWH015, JWH133, LY2828360, MDA7, MDA19
CB1/CB2 agonists	BAY59-3074, CP55,940, CT-3, HU-210, O-1602, WIN55,212-2
CB1 antagonists	AM251, SRI41716
CB2 antagonists	AM630, SRI44528
Uptake inhibitors	AM404, LY2183240, VDMI1
FAAH inhibitors	AA-5-HT, ASP8477, PF-3845, ST4070, OL-135, URB597, URB937
MGL inhibitors	JZL184, KML29, MJN110, URB602
FAAH/MGL inhibitors	JZL195, SA-57

**Abbreviations:** AEA, *N*-arachidonylethanolamine; CB, cannabinoid; CBD, cannabidiol; FAAH, fatty-acid amide hydrolase; MGL, monoacylglycerol lipase; NP, neuropathic pain; THC, tetrahydrocannabinol.

mediated through cannabinoid receptors,<sup>51,53,68,75–77</sup> interacting with spinal mGlu5 receptors,<sup>78</sup> 5-HT<sub>1A</sub> receptors,<sup>79</sup> posterior inhibition of p38 MAPK/NF- $\kappa$ B activation and cytokine release,<sup>68</sup> GPR55 activation<sup>75</sup> and stimulating endogenous norepinephrine release.<sup>80</sup>

Inflammation has also been shown to be involved in the development of NP,<sup>81</sup> and cannabinoid agonists may abolish the increased levels of mediators known to be involved in NP, such as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), NO and the neuronal NO synthase.<sup>54</sup> All these mediators may lead to attenuate the early production of spinal proinflammatory cytokines interleukin (IL)-1 $\beta$ , IL-6 and tumor necrosis factor (TNF)- $\alpha$ .<sup>62</sup> SR141716 (rimonabant), an antagonist/inverse agonist of CB<sub>1</sub> receptor, has also exerted antihyperalgesic activity in the chronic constriction injury model by reducing the levels of TNF- $\alpha$ , PGE<sub>2</sub>, lipoperoxide and NO<sup>45</sup> in diabetic neuropathy.<sup>82,83</sup>

Cannabinoid receptor agonists have been suggested to have good analgesic efficacy in animal models of NP, but their use is limited by motor and psychotropic side effects. It has been proposed that these side effects might be overcome by using agents that indirectly activate the endocannabinoid system.<sup>84,85</sup> Substances inhibiting the reuptake of endocannabinoids<sup>86–88</sup> or inhibiting the FAAH and MGL, degradation enzymes of the two major endocannabinoids – anandamide or 2-AG, respectively, have found to be effective in the attenuation of neuropathy.<sup>84,89–95</sup> On the other hand, selective FAAH and MGL inhibitors were suggested to have a better therapeutic window than cannabinoid agonists, but they exerted lesser efficacy in these pain models. For instance, the FAAH inhibitor PF04457845 has not progressed through human chronic pain studies because of poor efficacy.<sup>96</sup> However, dual inhibitor of FAAH and MGL or a combination of FAAH inhibitor with a low dose of the MAGL inhibitor had greater anti-allodynic efficacy than selective FAAH or MGL inhibitors plus a greater therapeutic window than a cannabinoid receptor agonist.<sup>84,85,94</sup>

The abovementioned data indicate that endocannabinoids modulate pain under physiological conditions, and the high amount of preclinical evidence reports the antinociceptive effects of cannabinoids in NP. All these observations have led clinicians to start clinical trials using cannabinoids for the treatment of chronic pain.<sup>38,97</sup> For instance, Sativex (nabiximols) is prescribed for the symptomatic relief of NP in adults with multiple sclerosis and as an adjunctive analgesic treatment for adult patients with advanced cancer,<sup>98</sup> and nabiximols has been approved as a botanical drug in the UK in 2010 as a mouth spray to alleviate NP, spasticity, overactive bladder and other symptoms associated with multiple sclerosis.<sup>99,100</sup>

## Antinociceptive effects of cannabinoids in cisplatin-induced NP

Considering their antinociceptive effects in NP, cannabinoids are also evaluated in the animal model of cisplatin-induced neuropathy. Cisplatin has been shown to alter endocannabinoid tone,<sup>95</sup> and inhibition of endocannabinoid hydrolysis by FAAH and MGL inhibitors<sup>95</sup> or administration of cannabinoid agonists produced antinociceptive effects.<sup>63,70</sup> AM1710, a cannabimimetic CB<sub>2</sub> selective agonist, produced CB<sub>2</sub>-mediated suppressions of mechanical and cold allodynia induced by cisplatin.<sup>101</sup> Administration of the FAAH inhibitor URB597 into the receptive field of sensitized C-fiber nociceptors decreased spontaneous activity, increased mechanical response thresholds and decreased evoked responses to mechanical stimuli, which were mediated primarily by CB<sub>1</sub> receptors.<sup>102</sup> CBD and  $\Delta$ -9-THC attenuated cisplatin-induced tactile allodynia, but they could not prevent cisplatin-induced neuropathy when administered prophylactically.<sup>66</sup> Co-administration of JZL184, an inhibitor of endocannabinoid 2-arachidonoyl-sn-glycerol, with cisplatin blocked mechanical hyperalgesia, which might result from downstream activation of CB<sub>1</sub> receptors.<sup>103</sup> In our studies, concurrent,<sup>104,105</sup> but not acute,<sup>106</sup> administration of anandamide or agmatine attenuated neuropathy. Cisplatin also had concentration-dependent neurotoxic effects on DRG in vitro, and a high concentration of anandamide attenuated cisplatin neurotoxicity.<sup>106</sup>

## Agmatine: history and pharmacological importance

Agmatine, 4-aminobutyl guanidine, is an endogenous amine that was first discovered and purified from herring sperm ~100 years ago by Kossel.<sup>107</sup> It is widely distributed in many tissues including brain, stomach, intestine and aorta.<sup>108</sup> Agmatine is synthesized following decarboxylation of L-arginine by arginine decarboxylase.<sup>109</sup> Agmatine was thought to have an important role in arginine and polyamine metabolism, and at first was only attributed to bacteria<sup>110,111</sup> and plants.<sup>112</sup> However, in 1994, agmatine was purified from bovine brain as a clonidine-displacing substance and called endogenous ligand for the imidazoline receptors.<sup>113</sup> It is expressed in the central nervous system and meets most of the criteria of a neurotransmitter/neuromodulator.<sup>111</sup> Agmatine antagonizes N-methyl-D-aspartic acid (NMDA) receptors, inhibits competitively all isoforms of nitric oxide synthase (NOS)<sup>110</sup> and binds to  $\alpha$ <sub>2</sub>-adrenoceptors, imidazoline receptors as well as 5-HT<sub>3</sub> and nicotinic acetylcholine receptors with moderate

affinity.<sup>109,111,113</sup> It has several biological functions such as cognitive, anxiolytic, antidepressant, antiproliferative properties against tumor cells and neuroprotective properties.<sup>114–116</sup> Agmatine also modulates morphine dependence and tolerance.<sup>117</sup>

## Antinociceptive effects of agmatine in animal models of NP

Agmatine has produced antihyperalgesic and antiallodynic effects in animal models of chronic neuropathic and inflammatory pain. Intrathecal injection of agmatine increased dose-dependently morphine analgesia and potentiated acutely delta opioid receptor-mediated analgesia.<sup>118</sup> Its peripheral administration was shown to enhance the antinociceptive effect of co-administered morphine through  $\alpha_2$ -adrenoceptor-mediated mechanism.<sup>119</sup> Agmatine antagonized some hyperalgesic states;<sup>119,120</sup> reversed inflammation-, spinal cord injury- and nerve injury-induced pain<sup>121</sup> and attenuated the streptozotocin-induced<sup>122</sup> and sciatic nerve ligation-induced NP.<sup>123</sup>

In diabetic neuropathy, L-arginine supplementation has been shown to prevent the development of mechanical hyperalgesia and tactile and thermal allodynia with concomitant reduction of NO.<sup>124</sup> It was also shown that spinal agmatine produced antiallodynic and antihyperalgesic effects in diabetic neuropathy involving the imidazoline receptors.<sup>125</sup> In diabetes mellitus (DM), oxidative and also nitrosative stress induced by persistent hyperglycemia is considered as one of the pivotal contributors in DM-associated neural dysfunction.<sup>126</sup> Elevated oxidative stress leads to vascular dysfunction with ensuing endoneurial hypoxia, which causes impaired motor and sensory nerve functions.<sup>127</sup> In addition, L-arginine deficiency was also reported in streptozotocin-induced diabetes in rats.<sup>128</sup> NO, agmatine and glutamate share common NMDA receptor-mediated effects in the central nervous system. These underlying mechanisms may be responsible for the antinociceptive effects of agmatine in diabetic neuropathy.

Traumatic nerve injury also induces chronic pain and may trigger common, secondary pathological cascades, including activation of NMDA receptor,<sup>129</sup> AMPA/kainate receptors<sup>130</sup> and NOS.<sup>131</sup> NMDA receptor activation increases intracellular  $Ca^{+2}$ , which activates NOS to produce NO from L-arginine. NMDA receptors are known to have an important role in chronic pain processing from peripheral nerve injury. In sciatic nerve ligation-induced NP model, agmatine attenuated NP,<sup>118,122</sup> which may involve the reduction of NO levels and noradrenergic activity in the brain.<sup>118</sup> These beneficial effects of agmatine may partly result from the participation

of noradrenergic neurons in the locus coeruleus involved in the development and/or maintenance of allodynia and hyperalgesia in the setting of peripheral nerve injury.<sup>132</sup> Agmatine can bind to  $\alpha_2$  and imidazoline (1) receptors. An imbalance of supraspinal inhibition and facilitation was suggested to play a role in neuropathic hypersensitivity.<sup>132</sup> The locus coeruleus was reported to contribute to bidirectional modulation of pain.<sup>133</sup> It was shown that noradrenergic locus coeruleus lesions inhibited the development of allodynia and hyperalgesia and noradrenergic reuptake inhibitors decreased NP.<sup>134</sup> Although the locus coeruleus seems as a pain inhibitory structure,<sup>133,135</sup> there are some results indicating that it could participate in the facilitation of NP. The coeruleospinal noradrenergic fibers were suggested to be involved in descending inhibition of spinal pain transmission.<sup>136</sup> Agmatine was demonstrated to reduce norepinephrine and 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) levels in the brainstem and lead to increased pain threshold in NP.<sup>123</sup> The decreased central noradrenergic activity by agmatine via presynaptic  $\alpha_2$ -adrenoceptor activation was suggested to involve in the relief of NP.<sup>123</sup> Additionally, it was also reported that  $\alpha_2$ -adrenoceptor activation leads to release of acetylcholine and mechanical hyperalgesia is inhibited via muscarinic receptors at spinal levels.<sup>137</sup>

The antihyperalgesic effect of agmatine probably involves spinal imidazoline (1) receptors. It was reported that an imidazoline (1) receptor antagonist could reduce the antiallodynic and antihyperalgesic activities of agmatine in diabetic NP.<sup>125</sup> In addition, agmatine has also an antiallodynic effect in both animal models of NP with spinal nerve ligation and diabetes.<sup>122</sup>

In regard to all underlying mechanisms of NP, agmatine can partly overcome different kinds of neuropathies considering its NMDA receptor antagonist, NOS inhibitory and anti-inflammatory activities.<sup>121</sup> Neuronal injury and chronic pain can trigger several pathological cascades including stimulations of NMDA receptors and NOS.<sup>129</sup> Agmatine was shown to inhibit NMDA receptors, NMDA-mediated  $Ca^{2+}$  currents and also all isoforms of NOS, most potently inducible forms.<sup>110,138</sup> Recently, we also demonstrated that agmatine could prevent cisplatin-induced mechanical allodynia and degeneration of DRG cells and sciatic nerves. Our results showed that L-NAME did not significantly potentiate the antiallodynic and neuroprotective effects of agmatine.<sup>139</sup> It was demonstrated that NOS inhibitors and NMDA receptor antagonists could increase the release of 5-HT by activating tryptophan hydroxylase.<sup>140</sup> It can be thought that the increase in serotonin could contribute the antinociceptive activity of agmatine.

Since microglial and astrocytic cells release neurotrophic factors that have proinflammatory and neuroprotective effects, it was also suggested that macrophages, activated microglia and infiltrated monocytes have a major role in neuroinflammation.<sup>141</sup>

It was suggested that agmatine might increase the anti-inflammatory M2 macrophage properties without enhancing cell numbers.<sup>142</sup> This can also contribute to its activity against neuropathies, considering the proinflammatory M1 and anti-inflammatory M2 macrophages-induced promotion of axonal regeneration after neuronal injury.<sup>141,143</sup>

Furthermore, agmatine is widely distributed in several brain regions including hippocampus and co-localized with sigma receptors.<sup>108</sup> Sigma receptors were also found in sciatic nerves,<sup>144</sup> and especially, sigma 1 receptors had a role to modulate NP.<sup>145</sup> Additionally, there are some reports to suggest the elevation of hippocampal TNF- $\alpha$  levels in NP.<sup>146</sup> The agonists of sigma 1 and sigma 2 receptors were found to stimulate the production of TNF- $\alpha$ , and agmatine decreased the levels of TNF- $\alpha$ , suggesting to block these receptors in NP-induced rats.<sup>147</sup>

Therefore, the antinociception caused by agmatine may involve opioidergic, serotonergic,  $\alpha_2$ -adrenergic, imidazole<sup>148</sup> and opioidergic sigma receptors,<sup>147</sup> which were recently reported to play an important role in antinociceptive activity of agmatine in NP.<sup>143</sup> These predictions need further investigations.

## Conclusion

NP arises through multiple and complex mechanisms. The use of animal models helped to understand the pathophysiological mechanisms and to better define the treatment targets. Many scientific investigations on the effects of cannabinoids and agmatine on NP are now available considering endocannabinoid system's involvement in NP and agmatine's multiple targets, which are also implicated in NP, and give rise to new therapeutic opportunities. Cannabinoid ligands could open future perspectives for NP management, but their potential harms should be outweighed. At this point, substances that indirectly activate the endocannabinoid system with inhibition of the reuptake of endocannabinoids or degradation enzymes might be promising with less side effects. Furthermore, experimental studies indicate that agmatine gives great promise for the development of an improved treatment of this common disease. At the same time, agmatine has been shown to have a good safety profile with no effect on behavior, locomotion, or cardiovascular functions in naive animals.<sup>149</sup>

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## Disclosure

The authors report no conflicts of interest in this work.

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