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The role of opioid and nitrergic systems in dual modulation of seizure susceptibility

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Abstract

Epilepsy is a chronic disorder presented by recurrent episodes of seizures and affect worldwide individuals. The underlying mechanism of seizure is still elusive. Hence, there is still a need to determine the contribution of various systems in neurobiology and treatment of seizure. Evidence shows that opioid and nitrergic systems within the brain interact to modulate various physiological and pathological conditions including memory, pain, reward, addiction, depression, and seizure. Various studies revealed that diverse dose of opioids such as morphine has dual modulation in seizure susceptibility. For instance, it is reported that morphine at lower doses (0.5, 1, and 3 mg/kg) exerts an anticonvulsant effect in experimental seizure models, whereas at higher doses (15, 30, and 60 mg/kg) it could exacerbate the seizure. Similarly, nitrergic system has also been observed to possess dual effects in modulating the seizure threshold. Therefore, understanding of opioidergic and nitrergic systems interaction in seizure seems important to achieve the successful goal of seizure management. This review aimed to clarify and provide insight into how opioidergic and nitrergic systems interact in brain and mediate seizure behavior.

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Introduction

Opioid system is a complex system involved in a diverse range of homeostatic functions. It is highly expressed throughout the brain, spinal cord, peripheral nervous systems, and in various other tissues. Interaction of various agents with endogenous opioids could cause both beneficial and adverse effects. Currently, its physiological and pharmacological effects are attributed by the activity of its three distinct receptors, mu, delta, and kappa. All are G protein-coupled receptors and are expressed both in presynaptic and postsynaptic neurons. Endogenous opioid peptides such as dynorphins, endorphins, enkephalins and the exogenous alkaloids such as morphine can activate these receptors. Recent research has reported new information on opioid receptor-mediated activities and their underlying phenomena with reference to seizure threshold. Opioid system involved in seizure modulation is extremely complex as both proconvulsant and anticonvulsant actions have been reported. Our previous experiments have revealed the involvement of specific opioid receptors in the proconvulsant and anticonvulsant effects, which are linked to interaction of opioids with nitric oxide (NO) system [1-10]. Therefore, information about the effects of this system is useful in understanding the susceptibility of seizure to various drugs and their doses, as well as the possible interaction with NO system. The present review aims to discuss the underlying mechanisms of opioids and NO system in seizure and finally to rearrange these pleiotropic actions in a comprehensive way.

Methods

Literature search strategy and selection criteria

Literature concerned to these systems with their possible interaction was sorted out using key words such as morphine, opioids, nitric oxide and seizure in google scholar and web. The relevant literature based on their contents was selected and was pen down into this comprehensive and conceptual review.

Discussion

Opioids and epileptic seizures

The effect of opioids on epileptic seizures is still controversial. Both proconvulsant and anticonvulsant effects of opioids such as tramadol [11] and morphine have been reported to be mediated by μ-(mu), δ-(delta), and κ-(kappa) opioid receptors (MOR, DOR, KOR, respectively) in various species including rats [12], human being [13], mice [14], and monkeys [15]. Rubaj etal. highlighted that normobaric hypoxia can reduce the susceptibility to pentylenetetrazole (PTZ)-induced convulsions, which could be mimicked by μ-or κ-receptor agonists in the brain [16]. In experimental epileptic models, it has been shown that epileptic seizures upregulate the opioid receptors [17], and potentiate the levels of endogenous opioid like enkephalins and dynorphins in the brain [18,19]. Opioids might possess anticonvulsant or proconvulsant effects in a dose-dependent manner in the brain. For instance, other extensive studies confirmed that at low concentration, morphine diminishes the electrographic seizure, while exacerbates seizure activity in high concentrations [20]. In addition, in some early studies, it was found that opioids inhibit the inhibitory interneurons, which thereby exacerbate the epileptic seizure rather than inhibiting it. DOR exerts suppressive epileptic activities in cortical regions trough inhibiting sodium channels. Interestingly, researchers have reported that if DOR is down-regulated and sodium channels are up-regulated, then it will exacerbate epilepsy [21,22]. It is also stated that α_2-adrenoceptors play a dramatic role in modulating the anticonvulsant effects of morphine. In addition, agmatine that is considered to be used as an adjunct therapy for seizure, enhances the anticonvulsant effect of morphine through α_2-adrenoceptors [23]. Lipopolysaccharide has been found to facilitate seizure susceptibility in colonic seizure model of mice. This activity was facilitated by opioid system along with other molecules such as prostaglandins and NO [24].

Morphine and endogenous opioids possess anticonvulsant effects

Morphine is the main psychoactive chemical agent in opium used in certain clinical conditions. Since its discovery dates back to almost 210 years ago, it was found that morphine exhibits anticonvulsant effect. Some clinical trials report the anticonvulsant properties of morphine as well [25]. Various experimental studies have also shown the anticonvulsant effects of morphine. For instance, morphine was found to delay the onset of PTZ-induced seizures in experimental animal models of seizure [1]. These results were further confirmed by the study where the subcutaneous administration of acute lower doses of morphine (0.5, 1, and 3 mg/kg) postponed the onset of PTZ-induced seizure [7]. Similarly, morphine decreases the intensity of maximal electroshock seizures[26]. Acute doses of morphine also illustrate an anticonvulsant effect against various seizure models induced by gamma-Aminobutyric acid (GABA) transmission blockers, such as picrotoxin, bicuculline, PTZ, and isoniazid [27]. Similar to morphine, other opioids such etorphine and β-endorphin also increase the seizure threshold and demonstrate anticonvulsant effects [28,29]. Different species may respond asymmetrically to these effects. For example, morphine acts as a proconvulsant to PTZ-induced seizure model of mice [30], while on the contrary, it might act as an anticonvulsant following PTZ administration in rat model [31].

Morphine and endogenous opioids possess proconvulsant effects

Previously, it was reported that morphine under certain conditions, shows anticonvulsant effects. However, in contrast, morphine also exerts proconvulsant effects under certain conditions, for instance, when a high systemic dose of morphine is used. Data from the previous research, found that epileptiform patterns and behavioral convulsions may be exacerbated by high doses of morphine in various experimental animals such as rabbits [32], mice [30], monkeys [33], and even in humans. Morphine can also initiate electrographic

seizures in rats following intracerebroventricular injection at high doses [34]. We also reported that apart from the proconvulsant behavior, morphine when used in subeffective proconvulsant dose, could enhance the proconvulsant effects of Sildenafil [14]. Surprisingly, we showed that injection of anticonvulsant dose of morphine (1mg/kg) in post weaning social isolation stress model in mice, exerts proconvulsant effects. It might be due to dysregulation of opioid system in these animals induced by social isolation stress thus mediating the opposite response [35]. Considering the diversity of proconvulsant and anticonvulsant effects of morphine we can assume that these opposite effects might be mediated through different mechanisms, sites, and receptors. Table 1 shows anticonvulsant and proconvulsant properties of opioids.

Opioid receptors and seizure

Opioid receptors are expressed in different parts of the brain. In majority of experimental models of seizure, both the proconvulsant and anticonvulsant effects are shown to be linked with these receptors. Morphine exerts both anticonvulsant (1, 3, and 7.5 mg/kg, i.p.) and proconvulsant (30 and 60 mg/kg, i.p.) effects in similar seizure models. In addition, we showed that glibenclamide at higher doses (2.5-5 mg/kg) amplified the PTZ-induced seizure threshold, while in lower dose (1 mg/kg) interestingly suppressed both anticonvulsant and proconvulsant effects of morphine. However, cromakalim (1 µg/kg) reversed these responses [36]. There is well-documented interaction between endogenous opioids and cannabinoids [37]. Cannabinoids itself is thought to participate in susceptibility of seizure in various animal models. The opioid receptors antagonist, naltrexone or cannabinoid CB1 receptor inverse agonist could reverse the increased seizure threshold, which might be attributed either by GABAergic synapses up-regulation or down-regulation of glutamate synapses [38]. This question needs to be addressed that why the different doses of the same drug make different responses, while interacting with same opioid system. Answering this question may open new ways to development of new efficient therapeutic targets in seizure treatment.

Opioid receptors involved in anticonvulsant effects

Evidence shows the involvement of opioid receptors in anticonvulsant effects of opioids. For example, it is reported that dynorphin regulates the hippocampal excitability, thereby producing anticonvulsant effects by interacting with KOR [39]. We previously showed that anticonvulsant effect of a low dose of morphine(100µg/kg) was significantly boosted by systemic administration of low dose of the opioid receptor antagonist, naltrexone (10 mg/kg) [5]. It is also reported that selective MOR antagonist cyprodime (3mg/kg,i.p.) and opioid antagonist naltrexone (0.3, and 1mg/kg,i.p.) markedly inhibited the increase in electroshock seizure threshold, which was induced by phenytoin (3mg/kg,i.p.) [40]. Our lab also reported that in cholestatic mice, the levels of endogenous opioids increase, which boost the PTZ-induced seizure threshold in cholestasis [3].

Opioid receptors involved in proconvulsant effects

Different opioid receptors are involved in mediating the proconvulsant effects of morphine and other related opioids. It is reported that neuroexcitatory action of morphine in spontaneous seizure activity is mediated via selective stimulation of the MOR and KOR subtypes, but not by DOR subtype [20]. We have shown that subcutaneous administration of morphine increased sensitization to PTZ-induced clonic seizures through interaction with MOR [41]. These findings were replicated in our further experiments [1,42]. However, some investigators disproved this hypothesis and reported an increase in proconvulsant effects of the opioid antagonist. Thus, after systemic administration of morphine, nalorphine in spite of blocking the behavioral convulsions in mice and rats, shortened the onset of seizure [43,44]. The levels of sex hormones affect the seizure threshold as for instance, in our study we reported that diestrus mice are more susceptible to anticonvulsant effect of morphine [45]. It shows that sex difference may also have some effects on opioids in modulating seizure. Convulsions also occur because of hyperactivity of N-methyl-D-aspartate (NMDA) receptor in MOR knockout mice. In MOR knockout mice, it was found that activity of NMDA receptor is increased in thalamus, hypothalamus, and parietal cortex, which resulted in increase in synaptic excitability convulsions [46].

Opioids and nitric oxide (NO) interaction

Opioids along with NO possess dramatic role in various biological functions such as pain, reward, addiction, depression, and seizure [47-54]. Opioid system interacts with NO in certain physiological functions. NO is an unstable signaling molecule helpful in implicating diverse physiological functions such as memory, learning, and neurogenesis, as well as seizure, depression, and other neurological disorders [55-58]. It is formed from L-arginine endogenously by various isoforms of nitric oxide synthase (NOS) enzymes expressed in different parts of the body including brain [59-61]. Some reports including from our lab demonstrated that NO and opioids interact together in various conditions including memory, ethanol gastric damage, cholestasis, morphine tolerance, pain, and seizure [1,10,47,48,61-77]. In seizure, the effect of NO are still unclear as it shows ambiguous activity in seizure modulation when interacting with opioids and their receptors. It has been shown that under certain laboratory protocol for seizure, NO may mimic the anticonvulsant effects of opioids, while in other set of conditions, it reverses the anticonvulsant properties of opioids [3,9]. We also obtained similar results using different doses of opioids and its interaction with various receptors [6,8]. Moreover, we reported that co-administration of subeffective doses of morphine (0.1 and 0.5 mg/kg) with the NOS inhibitor, Agmatine (3 mg/kg) enhances anticonvulsant effects, while the NO precursor, L-arginine (30 and 60 mg/kg) reverse this

response. This shows that agmatine boosts the anticonvulsant effects of morphine through NO pathway in experimental seizure model in mice [78]. Similarly, it was shown that proconvulsant effects of chloroquine are mediated through opioid system and neuronal nitric oxide synthase (nNOS) enzyme [79]. Hence, these reports confirm that there is a strong co-relationship between opioidergic and nitrergic systems in modulation of seizure susceptibility. Some evidence shows an ambiguous effect of opioids on NOS activity. However, most opioids (MOR and DOR agonists) stimulate NOS activity [61,80,81], while KOR agonists are reported to inhibit the activity of NOS [82,83]. Figure 1 illustrates the interaction between opioids and NO.

Nitric oxide and its effect on seizure threshold

Epilepsy comprises a group of related disorders characterized by a tendency for recurrent seizures. NO is retrograde neurotransmitter that regulates brain excitability and seizure threshold in various experimental models of seizure [84]. Research from our laboratory show the involvement of NO in modulation of seizure susceptibility using various drugs treatment. We recently found that NO plays a crucial role in serotonin-5-HT_3 receptor activation, which leads to anticonvulsant responses in PTZ-induced seizure [85,86]. Furthermore, our recent experiment revealed that NOS inhibitors, L-NG-Nitro arginine methyl ester (L-NAME) and 7-Nitroindazole (7-NI) alone or in combination with low dose of 5-HT_3 receptor agonist enhanced anticonvulsant properties of citalopram, which corroborated our aforementioned studies [87]. In addition, the possible role of peroxisome proliferator-activated receptor gamma (PPAR-γ) and NO pathway in PTZ-induced seizure has been reported. Using PPAR-γ agonist exerted anticonvulsant effect while PPAR-γ antagonist or L-NAME could reverse this effect. Hence, it implicate the involvement of NO system in this response [88]. Additionally, recently it was reported that hippocampal NO levels are involved in proconvulsant effects of social isolation stress (SIS) in postnatal mice [89].

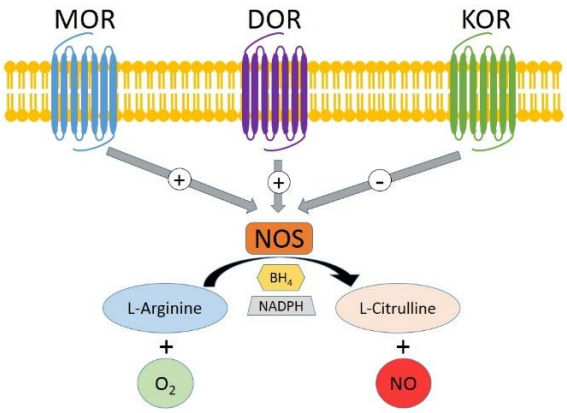

Figure 1: Opioids and Nitric oxide interaction. MOR: mu opioid receptor, DOR: Delta opioid receptor, KOR: Kappa opioid receptor, NOS: Nitric oxide synthase, BH_4: Tetrahydrobiopterin, NADPH: Nicotinamide adenine dinucleotide phosphate, NO: nitric oxide.

Proconvulsant effects of Nitric oxide

NO exerts both proconvulsant and anticonvulsant activities in seizure occurrence. Most of literature review reports the proconvulsant effects of NO. For instance, we have shown that anticonvulsant effects of thalidomide is mediated by modulation of nNOS enzyme [90]. Similarly, evidence show that NOS inhibitors such as L-NAME diminish the seizure induced by cocaine or NMDA [91,92]. Akula *et al*. showed that the NO precursor, L-arginine reverses the anticonvulsant effect of adenosine, while on the other hand, NOS inhibitors, L-NAME and 7-NI potentiate this effect [93]. An interesting research about the sex differences in seizure susceptibility revealed that NO mediate seizure in both sexes, while males are more susceptible to seizure [94]. Licofelone as a dual cyclooxygenase (COX) /5-lipoxygenase (5-LOX) inhibitor is recently reported to possess analgesic and anti-inflammatory properties. Our recent experiment also revealed the neuroprotective and anticonvulsant effects of this agent through downregulation of inducible nitric oxide synthase (iNOS) enzyme [95]. We also reported that the COX-2 inhibitor, celecoxib exerts an anticonvulsant effect in clonic seizure threshold through inhibition of NO pathway [96].

Anticonvulsant effects of nitric oxide

Beside the proconvulsant affects of NO, various investigations have reported the anticonvulsant actions of this neurotransmitter. Starr *et al*. reported that NO normally suppresses epileptogenesis in pilocarpine-induced limbic epilepsy in mice [97]. Buisson *et al*. have also shown that injection of NOS inhibitors deteriorates the seizure induced by intracerebroventricular injection of NMDA [84]. It is suggested that NO can increase the cerebral blood flow and acts as anticonvulsant in bicuculline-induced seizure [98]. It was also shown that α-tocopherol could reverse penicillin-induced epileptiform electrocorticographical activity in rats through NO formation [99]. Moreover, we reported that cannabinoid CB1 receptor agonist postponed the occurrence of PTZ-induced seizure through nitrergic system [100]. We also showed that neuroprotective and anticonvulsant properties of acute and chronic administration of atorvastatin in electroshock and PTZ seizure models is at least in part due to iNOS activity [101,102]. Our recent experiments concluded that acute and subchronic administrations of the antipsychotic agent, aripiprazolein chemically- and electrically-induced seizures in mice are linked to release of NO induced by iNOS and nNOS enzymes [103,104]. Hence, this literature review suggests that NO possesses anticonvulsant properties too. Table 2 demonstrates proconvulsant and anticonvulsant properties of NO.

Opioids/Nitric oxide and seizure

Opioidergic and nitrergic systems are among the highly studied systems which affect seizure threshold. Evidence shows the correlation between opioidergic and nitrergic systems in dual modulation of seizure by various drugs. Research from our laboratory revealed that

Species	Seizure induction model	Drug	Dose	Results	Reference
Mice	PTZ	Morphine	1 mg/kg, IP	Anticonvulsant	[1]
Mice	PTZ	Morphine	0.5-3 mg/kg, SC	Anticonvulsant	[7]
Mice	Electrical	Morphine	0.001-10 mg/kg, IP	Anticonvulsant	[26]
Mice	PTZ	Morphine Fentanyl Pethidine	20 mg/kg 250 µg/kg 100 mg/kg	Anticonvulsant	[106]
Mice	Bicuculline	Morphine Fentanyl Pethidine	20 mg/kg 250-500 µg/kg 25-100 mg/kg	Anticonvulsant	[106]
Mice	NMDA	Morphine Fentanyl Pethidine	5-20 mg/kg 125-250 µg/kg 12.5-100 mg/kg	Anticonvulsant	[106]
Mice	Kainic acid	Morphine Fentanyl Pethidine	20 mg/kg 500 µg/kg 100 mg/kg	Anticonvulsant	[106]
Rats	Flurothyl	Etorphine	0.05–1.6 µg, ICV	Anticonvulsant	[28]
Gerbils	Genetic	β-endorphin	0.1–3 µg, ICV	Anticonvulsant	[29]
Rats	PTZ	Morphine	5-15 mg/kg, IP	Anticonvulsant	[31]
Mice	-	Morphine	15-100 mg/kg, IP	Proconvulsant	[30]
Mice	-	Morphine	30 mg/kg, IP	Proconvulsant	[1]
Rats	-	Morphine	10 mg/kg, IP	Proconvulsant	[34]
Species	Seizure induction model	Drug	Dose	Results	Reference
Mice	PTZ	Morphine	1 mg/kg, IP	Anticonvulsant	[1]
Mice	PTZ	Morphine	0.5-3 mg/kg, SC	Anticonvulsant	[7]
Mice	Electrical	Morphine	0.001-10 mg/kg, IP	Anticonvulsant	[26]
Mice	PTZ	Morphine Fentanyl Pethidine	20 mg/kg 250 µg/kg 100 mg/kg	Anticonvulsant	[106]
Mice	Bicuculline	Morphine Fentanyl Pethidine	20 mg/kg 250-500 µg/kg 25-100 mg/kg	Anticonvulsant	[106]
Mice	NMDA	Morphine Fentanyl Pethidine	5-20 mg/kg 125-250 µg/kg 12.5-100 mg/kg	Anticonvulsant	[106]
Mice	Kainic acid	Morphine Fentanyl Pethidine	20 mg/kg 500 µg/kg 100 mg/kg	Anticonvulsant	[106]
Rats	Flurothyl	Etorphine	0.05–1.6 µg, ICV	Anticonvulsant	[28]
Gerbils	Genetic	β-endorphin	0.1–3 µg, ICV	Anticonvulsant	[29]
Rats	PTZ	Morphine	5-15 mg/kg, IP	Anticonvulsant	[31]
Mice	-	Morphine	15-100 mg/kg, IP	Proconvulsant	[30]
Mice	-	Morphine	30 mg/kg, IP	Proconvulsant	[1]
Rats	-	Morphine	10 mg/kg, IP	Proconvulsant	[34]

Table 1: Anticonvulsant and proconvulsant properties of opioids.

Species	Seizure induction model	Results	Reference
Mice	-	Proconvulsant	[90]
Rats	-	Proconvulsant	[91]
Mice	-	Proconvulsant	[92]
Mice	-	Proconvulsant	[93]
Mice	-	Proconvulsant	[94]
Mice	-	Proconvulsant	[95]
Mice	-	Proconvulsant	[96]
Mice	Pilocarpine	Anticonvulsant	[97]
Rats	Bicuculline	Anticonvulsant	[98]
Rats	Penicillin	Anticonvulsant	[99]
Mice	PTZ	Anticonvulsant	[107]

Table 2: Proconvulsant and anticonvulsant properties of Nitric oxide.

subeffective dose of lithium could inhibit both proconvulsant and anticonvulsant effects of morphine in clonic seizure threshold in mice. We suggested that blockade of opioid receptors signaling probably through activation of nitrergic system might mediate these effects of lithium [1]. We also showed that melatonin boosts both proconvulsant and anticonvulsant effects of morphine possibly through activation of nitrergic system. However, possible pharmacokinetic interaction between melatonin and morphine cannot be ruled out in enhancement of two opposing effects of morphine on seizure threshold [73]. Furthermore, the anticonvulsant effect of tramadol is mediated by activation of NO pathway through classic opioid receptors [105].

Conclusion

This review has focused on the interaction between opioid and nitrergic systems in modulating the seizure threshold in various experimental paradigms of seizure. Such information could clarify that how seizures respond to different opioids and what is the impact of NO levels on seizure threshold. Morphine exerts dramatic proconvulsant and anticonvulsant effects depending on dose and conditions. It is concluded that morphine can provoke electrogenic convulsions when administered

systemically in high doses. This effect seems to be initiated by another system rather than opioid receptors, since opioid antagonist fails to reverse it. Pharmacological evidence supports that intracerebroventricular injection of morphine triggers convulsive behavior through MOR and DOR opioid receptors. Conversely, the anticonvulsant effect of morphine is also reported to be mediated through MOR. Nitrergic system also exerts both proconvulsant and anticonvulsant effects for various drugs through different NOS isoenzymes in diverse animal models and conditions. Since, evidence show ambiguous results about the involvement of opioidergic and nitrergic systems in seizure mechanisms, site of action, and type of seizures, hence, this system is still highly challenging. Future investigations might elucidate the exact mechanisms explaining the anticonvulsant and proconvulsant effects of opioidergic and nitrergic systems interaction in seizure.

Authors' Contribution

MIK, FUS, AW: data collection and manuscript drafting, VN: tables and figures, ARD: study design and supervision.

Conflict of interest

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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