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Kappa Opioid Receptor Agonist and Brain Ischemia

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Abstract

Opioid receptors, especially Kappa opioid receptor (KOR) play an important role in the pathophysiological process of cerebral ischemia reperfusion injury. Previously accepted KOR agonists activity has included anti-nociception, cardiovascular, anti-pruritic, diuretic, and antitussive effects, while compelling evidence from various ischemic animal models indicate that KOR agonist have neuroprotective effects through various mechanisms. In this review, we aimed to demonstrate the property of KOR agonist and its role in global and focal cerebral ischemia. Based on current preclinical research, the KOR agonists may be useful as a neuroprotective agent. The recent discovery of salvinorin A, highly selective non-opioid KOR agonist, offers a new tool to study the role of KOR in brain HI injury and the protective effects of KOR agonist. The unique pharmacological profile of salvinorin A along with the long history of human usage provides its high candidacy as a potential alternative medication for brain HI injury.

Keywords

Kappa opioid receptor; Agonist; Brain ischemia; Neuroprotective

1 Introduction of Kappa opioid receptor agonist

1.1 Brief introduction of Kappa opioid receptor

The kappa opioid receptor (KOR), with mu (MOR), delta (DOR), and the nociceptin receptor (NOR) make up the opioid receptor (OR) system. Opioid receptors were proposed in the 1950s (1) and 1960s (2), and later found in mammalian brain tissue in 1973 using opioid radioligand binding assays (3-5). Subsequently, endorphins were discovered (6) and a variety of opioid receptors and subtypes have been identified. Although they are all receptors of opioid receptors, KOR is seemingly different from MOR and DOR. The heterogeneity of kappa binding sites in the brain membrane was evident by radioligand binding studies. Using some pharmacological agents, three main binding sites were identified as *K*1, *K*2 and *K*3 (7) and further subdivided into *K*1a, *K*1b, *K*2a and *K*2b (8). KOR cDNA clones have also been isolated and characterized from several species,

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including homo sapiens (9,10). KORs belongs to the class A (Rhodopsin-like) gamma subfamily of G protein-coupled receptors (GPCRs). They have a common seven-transmembrane helical architecture and are coupled predominantly to heterotrimeric Gi /G0 proteins (11). The crystal structures have disclosed a combination of key features shared with chemokine and aminergic GPCRs (12). For example, the opioids receptor (OR) share >40% structural homology with somatostatin receptors (SSTRs) and they are both expressed in some tumor tissues (breast cancer etc.) as negative regulators (13). KOR have a characteristic parallel-dimer in contact with helices I, II and VIII. Several distinct potential dimer interfaces of the KOR may serve to support its different functional pathway as well as promote oligomeric assembly of GPCRs (14).

1.2 Distribution of kappa opioid receptor

The radioligand binding method was widely applied to locate KOR in the brain (15-18). KORs are found in the following regions: the nucleus accumbens, caudate-putamen, olfactory tubercle, bed nucleus stria terminalis, medial preoptic area, paraventricular nucleus, supraoptic nucleus, hypothalamus, amygdala, midine thalamic nuclei, periaqueductal gray, raphé nuclei, parabrachial nucleus, locus coeruleus, spinal trigeminal nucleus, and the nucleus of the solitary tract (19). High levels of KOR mRNA were found using the human genomic sequence analysis and RT-PCR technology in ventral tegmental area (VTA), prefrontal cortex (PFC), hippocampus, nucleus accumbens (NAc), striatum, amygdala, locus coeruleus (LC), dorsal raphe nucleus (DRN), substantia nigra (SN), and hypothalamus in animal and human brains (10,20). Generally speaking, the KOR is spread throughout most of the entire central nervous system, and mainly found within the brain (hypothalamus, periaqueductal gray, and claustrum), spinal cord (substantiagelatinosa), and pain neurons, including peripheral and sensory neurons. Radioimmunology competitive binding assay and functional studies were utilized to determine the predominance of KOR in peripheral vessels among other opioid receptors (21,22).

1.3 Pharmacological effects of kappa agonists

Opioids have been used for centuries and many of their pharmacological effects have been identified. Opioids play important roles in processing pain and regulating many other aspects of physiological and pathological process, such as stress response, respiration control, gastrointestinal transit motility, endocrine regulation, immune function modulation, and mood regulation (23). Despite the high sequence homology and structure similarity, the KORs are distinguished from the other three opioid receptors by unique genes, tissue expression patterns, functional properties, and related side effects. KORs play important roles in the central nervous system without distinct euphoria or addiction that might be induced by mu agonists. Also, KORs plays a greater role than other opioid agonists in visceral pain models (24).

1.3.1 Antinociception effects—Although opiates are used as a painkiller targeting MORs in clinical practice, KOR agonist also exerts its effect in analgesia. Some advantages of KOR agonists over traditional opiates are the ability to suppress the drug reward response and antagonize various MOR-mediated actions in the brain. This includes tolerance, reward and memory process (25-30). Studies on opioid mechanisms provide evidence that the

opioid effect were through presynaptic and postsynaptic modulation of levels in some neurotransmitters, such as dopamine (DA), Gama-Amino Butyric Acid (GABA), and glutamate. Specifically, it could suppress the release of DA from the mesolimbic reward pathway and the nigrostriatal pathway (31). However, in the CNS, KOR agonists also produce some side effects such as dysphoria, sedation, diuresis, and respiratory depression, which limit their therapeutic usage in clinical practice(20).

1.3.2 Cardiovascular effects—Kappa and other opioid peptides are present in the heart; and KOR has been identified in pulmonary arteries. Myocardial cells are the site for opioid peptide synthesis, storage and release. Opioid peptide levels were elevated during episodes of stress, such as myocardial ischemia (32,33), and the expression of KOR increased during hypoxia (34). A recent study demonstrated the significant attenuation of the proliferation in pulmonary smooth muscle cells during hypoxic pulmonary artery hypertension (HPH) by a selective KOR agonist (U50,488H). U50,488H significantly increased the expression of KORs in the pulmonary artery during hypoxia and these effects can be abolished by Norbin, a KOR antagonist (35). We can expect the potential therapeutic strategy of KOR modulation in the treatment of pulmonary hypertension.

1.3.3 Antipruritic effects—KORs were found to have antipruritic effects, discovered in rodents (36-38) and humans (38,39). Nalfurafine hydrochloride was used in clinical practice to treat pruritus in hemodialysis patients in Japan (40).

1.3.4 Diuresis effects—Kappa agonists are also well recognized for their treatment in diuresis. Experimental designs have demonstrated the ability of KOR agonists to increase urine flow and decrease osmolality in animals [mice (41), dogs (42), monkeys (43)] and humans (44). Studies also showed that only some kappa agonists have this effect (e.g. nalfurafine, U50,488H, MOM-sal B) while absent in others (e.g. salvinorin A) (45). The mechanisms underlying the diuresis effects induced by kappa agonists are not clear, however, it is suggested to be through the suppression of vasopressin release.

1.3.5 Other effects—Kappa agonists are not limited to those listed above. It has also been utilized as an antitussive. Narcotic antitussives such as codeine, display the most potent effect with some CNS side effects primarily via the mu-opioid receptor (46).

1.4 Common kappa agonist

Some common KOR agonists are listed in Table 1. Dynorphins are the only endogenous ligands. Salvinorin A, obtained from a plant Salvia divinorum, originating in Mexico for religious purposes, has a high affinity and special selectivity for the KOR. Although, Salvinorin A is most known for its hallucinogenic effects, some reports have also showed its effect as an antidepressant, anti-inflammatory, and neuroprotection (47,48). Other highly selective kappa agonists such as U-50488H, U-69593, and BRL 52537 were widely used in experimental studies. Most of the selective kappa agonists available to date have been optimized at the K1 -binding site or the cloned *K1* receptor. There are also some unselective agonists such as Norbuprenorphine which acts as a μ-opioid, δ-opioid, and nociceptin receptor full agonist, as well as a κ-opioid receptor partial agonist (49).

2. Kappa opioid receptor agonist and brain ischemia

Brain ischemia generally means the lack of blood flow in brain tissues, which induces the alterations in brain metabolism and energy crisis. Also, brain ischemia leads to poor oxygen supply (hypoxia) and even cerebral infarction. The main symptoms of ischemia involve impairments in vision, body movement, and speaking. More specifically, unconsciousness, blindness, problems with coordination, and weakness of the body would occur in this process. Other consequences resulting from brain ischemia are stroke, cardio respiratory arrest, or other irreversible brain damages. Since stroke is a major public health burden in the world, there is a need for the development of theory-based interventions through behavioral changes that will reduce morbidity and mortality from strokes (50). KORs play an important role in modulating ischemic brain injury and several studies have shown that KOR agonists attenuated histologic brain injury (51-53) as well as improved functional recovery in animal models of global and focal cerebral ischemia (54-59).

Based on these, the role of the opioidergic systems in cerebral HI has been widely recognized. However, mechanisms in neuroprotection remain to be elucidated. Many experiments have been conducted to solve this problem using rat, mouse, rabbit, or piglet HI model with pre-treatment or post-treatment of KOR agonists. Several studies demonstrated the effects of KOR agonists in different animal models of global as well as focal cerebral ischemia.

2.1 The effect and mechanism of KOR agonist in global ischemia

In global ischemia, KOR agonist plays a role in attenuation of ischemia-induced hippocampal damage and cognitive impairment in rats (54,56). Recent studies showed that BRL52537 exerted neuroprotective effects on global ischemia (4-VO) partially through the up-regulation of p-STAT3 activation and down-regulation of caspase-3 (60). Some selective non-peptide KOR agonists such as U-50,488E and U-50,488H prevented brain edema and neuronal injury after transient global ischemia (61,62). Also, KOR agonists modulated glutamate excitotoxicity by inhibiting the increase of synaptosomal free Ca^{2+} levels and presynaptic glutamate release via closure of N-type Ca^{2+} channels and restriction of Ca^{2+} entry into presynaptic terminals (63-66). They also inhibited excitatory postsynaptic potentials through similar presynaptic mechanisms involving reduced nitric oxide (NO) production or modulating NMDA to induce dopamine release (67). Administration of Salvinorin A after global cerebral ischemia preserves vascular auto-regulation via KOR and extracellular signal-regulated kinase /mitogen-activated protein kinase pathway in piglets (68). It produced vascular dilation through activation of nitric oxide synthase and adenosine triphosphate-sensitive potassium channel (47).

2.2 The effect and mechanism of KOR agonist in focal ischemia

Highly selective KOR agonist had a wide therapeutic time window (at lease 6h) for neuroprotection after transient focal ischemia in a rat middle cerebral artery occlusion (MCAO) model (58). Such neuroprotective effects are receptor (54) and gender-specific (59), and associated with reduced neuronal nitric oxide (69). In addition, administration of U50,488H, a selective KOR agonist, before ischemia was shown to enhance blood flow after

occlusion with a significant drop in systemic blood pressure at a dosage of 30 mg/kg (70). U50,488 treatment reduced areas of severe tissue damage and increased areas of modest tissue damage which indicated that U50,488 prohibited the progression of damage from non-infarcted to fully infarcted tissue (71). Dynorphin A-(1-13), an endogenous KOR agonist, prolongs survival time in a focal cerebral ischemia model in cats and mice (55,72). The selective KOR agonist BRL52537 given as a pre-treatment or post-treatment in vivo attenuates ischemia-evoked NO production. The neuroprotection might be due to attenuation of the excitotoxic effects of NO from neuronal cells (58,59,69). Treatment with CI-977 (0.3 mg/kg, s.c.) 30 min before and 30 min after occlusion of the MCA reduced the infarct volume in the cerebral hemisphere (51). Another study on the neuroprotection effects of limb ischemic post-conditioning on rat brain ischemia/reperfusion injury showed that KOR and Mito K(ATP) might be involved in the process leading to the protective effect (73).

3. Major agonists and the related mechanism tested in different brain ischemic model

3.1 U-50,488E

U-50,488E, an analgesic agent with a specific agonist property on KOR, was found to be protective on bilateral carotid occlusion (BCO) in Mongolian gerbils and Fischer rats. Pretreatment (7 min before BCO) with U-50,488E reduced the development of behavioral hyperactivity and preserved the neurons of the hippocampus from ischemic cell death. Two other kappa opioid analgesics, ethylketocyclazocine and bremazocine, shared the effects of U-50,488E in the gerbils. On the other hand, naloxone and dynorphin have no protective effects in the same ischemic model (62).

3.2 U-50,488H

Pretreatment (4 h before BCO) with U-50,488H prevented the forebrain edema in a rat model. Administration of an antidiuretic hormone prevented the plasma hyperosmolarity and reduced the anti-cerebral edema properties of U-50488H. The plasma osmotic effect, however, may not completely account for such protective effects rendered by U-50,488H (61).

Also, U-50,488H (3 or 10 mg/kg i.v. doses) produced a significant improvement in early recovery in acute head and spinal injury models. (74). U-50,488H improved the memory functions in a transient forebrain ischemia model using a three-panel runway task. Administration immediately after reperfusion (i.p. 10 and 32 mg/kg) significantly reduced the amount of errors expected to occur in a working memory task assessed 24 h after 5 min of ischemia, indicating protective effects (75).

Not only could U-50,488H improve CBF in the ischemic brain of rats after MCAO, but it also had therapeutic potential in cerebral ischemia by attenuating Na(+)-K(+)-ATPase activity. U-50488H administration prevented the impairment of spontaneous alternation, the prolongation of transfer latency in elevated-plus maze, and the shortening of step-through latency in passive avoidance which is associated with the activation of KORs(70,76).

The effect of U50,488 was also studied at 6 h post-occlusion with permanent, unilateral occlusion of the internal carotid, middle cerebral, and anterior cerebral arteries via a trans-orbital, microsurgical approach in rabbits. While U50,488 did not improve survival rate, it reduced severe tissue damage (71).

3.3 Dynorphin

Handa evaluated the effect of dynorphin on improving neurological impairment using the inclined plane method with gerbil unilateral cerebral ischemia model (77).

Transient cerebral ischemia model in mice was used to test the effect of dynorphin A (1-13) on spontaneous alternation, elevated plus-maze performance and passive avoidance behavior. Prior to impairment, transient ischemic insult produced a marked memory dysfunction in mice and the i.c.v. injection of dynorphin A-(1-13) without affecting the body temperature (55,78).

Moreover, it has been demonstrated that endogenous dynorphin levels were increased in traumatic thoracic spinal cord injury in rats. The increased dynorphin was localized in the ischemic site and closely correlated with the damage and neurologic deficits (79). Dynorphin is considered to be the endogenous neuropeptide highly selective for kappa-opioid receptors.

3.4 GR89696

The protective effects of GR89696, a highly selective and potent KOR agonist, were observed in a transient bilateral carotid artery occlusion model in the Mongolian gerbil and a permanent MCAO model in mice. In the Mongolian gerbil model, administration of GR89696 immediately before and at 4 h after ischemia produced a dose-dependent reduction of neuronal loss in the hippocampal CA1 region. Similar effects were observed with two other kappa-agonists, GR86014 (1mg/kg, s.c.) and GR91272 (1mg/kg, s.c.). The neuroprotective effect of GR89696 was completely blocked by naltrexone, an opioid receptor antagonist. Repeated post-treatment with GR89696 (100μg/kg, s.c.) or GR44821 (10mg/kg, s.c.) protected ischemia-induced neurodegeneration in the hippocampal CA1 region. In the permanent, unilateral MCAO model in mice, 50% reduction in cortical infarct volume was observed with repeated GR89696 administration. GR89696 also produced a significant reduction in infarct volume when it was administered at 6 h after the insult, indicating a wide therapeutic window (52).

3.5 CI-977

The effect of CI-977 upon ischemic brain damage and brain swelling has been examined in rat and cat permanent occlusion of the middle cerebral artery (MCA) model. Treatment with CI-977 initiated 30 min or 15min prior to MCA occlusion produced dose-dependent reductions in the volumes of infarct and brain swelling (80,81), which is also related to the decreased level of extracellular glutamate, aspartate, and GABA observed in the focal ischemic penumbra (82). Subcutaneous administration of CI-977 at the induction of ischemia prevented neurodegeneration of CA1 and CA2 pyramidal neurons in the dorsal hippocampus of Mongolian gerbils transient forebrain ischemia (83). Also, CI-977 produced

dose-dependent reductions in the infarction volume and brain swelling in two acute rat models of focal cerebral ischemia [non-recovery (4 h) and recovery (24 h)] (84). However, CI-977 failed to produce statistically significant alterations in either the level of local CBF or on the volume of low CBF in the hemisphere ipsilateral to MCA occlusion, but areas of hyperemia were observed in both the medial caudate nucleus and lateral thalamus (51).

3.6 U-62,066E

U-62,066E showed neuroprotection against the hypoxia/hypoglycemia-induced deficit in glucose uptake (85). One review on U-62,066E reported that it could easily penetrate the blood brain barrier, and does not seem to have any significant active metabolites. The analgesic, antitussive, diuretic, and neuroprotective properties are well documented in mice and rats. Preclinical studies have shown that U-62,066E reduces blood pressure and heart rate, and has possible antiarrhythmic properties (86).

3.7 BRL 52537

BRL 52537 was reported to attenuate ischemia-evoked nitric oxide production in rats in vivo (56). Also, it has a neuroprotective effect against cerebral ischemia/reperfusion injury in rats and the underlying mechanisms involving the up-regulation of p-STAT3 and decrease in caspase-3 expression (87). It has been implicated to attenuate infarct volume in rat transient focal cerebral ischemia without producing post-ischemic hypothermia (54).

3.8 Salvinorin A

Salvinorin A (SA) is the only potent and highly selective KOR agonist that has been consumed by humans for several centuries with known safety profiles. But unlike other KOR agonists, salvinorin A does not produce any frank hallucination, and has no dysphoric actions (88). Some characteristic of this compound , such as the short-acting, quick onset, sedative effect, and no respiratory depression make it a suitable candidate for some urgency in clinical practice like stroke, cardiac arrest or asphyxia (89,90). Our previous study in piglets IR model showed that administration of SA 30 min before, immediately after and 30 min after reperfusion preserves cerebrovascular autoregulation and protects the neurovascular unit through extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) pathway (48,69). Also, it serves as a potent cerebral vascular dilator, under normal conditions or with constriction from endothelin and hypocarbia. The effect was produced via activation of nitric oxide synthase and adenosine triphosphate-sensitive potassium channel and opioid receptors (47,68,91). It is also reported that salvinorin A has ultra-potent effects on LPS-stimulated macrophages in vitro and effective in models of inflammation and inflammatory pain in vivo (92) and also works as an anti-inflammatory effect in experimental colitis in mice (93). So Salvinorin A might serve as a new anti-inflammatory agent targeting KORs and reduce the inflammatory reaction that happens commonly in ischemic brain injury. Although some neurologic effects of salvinorin A and its effect on global ischemia have been elucidated (94,95), no evidence exists for the effect and mechanism of salvinorin A on brain focal ischemic and reperfusion injury. Therefore, the physiologic profile and related mechanism should be well investigated to determine the maximum protective effect in brain ischemia.

4. Conclusion

The neuroprotective effects of KOR agonists against brain HI has the potential to reduce brain edema, infarction size and alleviate the neurological deficit with wide therapeutic window. However, the mechanisms of such protection are not fully elucidated and no medication for brain protection is available in clinical practice yet. The recent discovery of salvinorin A, a novel highly selective non-opioid KOR agonist without classic side effects of KOR agonist, offers a new tool to study the role of KOR during brain HI injury and the protective effects of KOR agonists. Its unique pharmacological profile with long history of human usage provides its high candidacy as a potential alternative medication for brain HI.

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Table 1

Categories of KOR agonists

Endogenous ligands	Selective agonists		Non-selective agonists
Dynorphins	U-50488	Asimadoline	Pentazocine
	GR89696	Cyclazocine	EKC
	CI-977	HZ-2	Etorphine
	U-62066E	ICI-204,448	Norbuprenorphine
	BRL 52537	ICI-199,441	Nalbuphine
	Salvinorin A	Levallorphan	
	Bremazocine	LPK-26	
	ICI-197067	BRL 52656	
	Ketocyclazocine	Menthol	
	Nalfurafine	Spiradoline	
	PD-117302	Niravoline	

KOR: Kappa opioid receptor