REVIEWS

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Models of neuroinflammation for the assessment of kappa-opioid receptor ligands

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The development of new drugs to combat neuroinflammation is highly relevant as it opens up possibilities for the treatment of a wide range of diseases, including Alzheimer's disease, Parkinson's disease, epilepsy, schizophrenia, depression, and others. Kappa-opioid agonists represent a promising class of compounds with a high potential to be used in the treatment of neurological conditions accompanied by neuroinflammation.

The aim of the study was to provide a summary of the current strategies employed to evaluate the neurotropic anti-inflammatory effects of kappa-opioid ligands in laboratory animals with induced neuroinflammation.

Materials and methods. The databases, such as Google Scholar, PubMed, ScienceDirect, Scopus, e-Library were used as search tools. The search comprised the following keywords and phrases in Russian and English: kappa opioids + neuroinflammation; kappa opioid receptors + neuroinflammation; neuroinflammation models; neuroinflammation models in rats, neuroinflammation models in mice. 148 relevant articles were found, 122 were included in this review.

Results. Various experimental models of neuroinflammation, including chemically-induced and bacterial endotoxin-induced neuroinflammation, as well as traumatic and genetic models in mice and rats were evaluated. In addition, the strengths and limitations of each model were critically assessed to identify the most appropriate and reliable approach for investigating the relationship between neuroinflammation and signaling pathways associated with kappa-opioid receptors.

Conclusion. The neurotropic anti-inflammatory activity of kappa-opioid ligands have been comprehensively described. The review discusses both experimental models where the effects of kappa-opioid agonists have been investigated, as well as the models where the anti-inflammatory properties of kappa-opioid agonists have not been studied yet.

Keywords: neuroinflammation; experimental models; neuroimmune processes; microglia; kappa-opioid receptors; kappa-opioid agonists; lipopolysaccharide

Abbreviations: Aβ – amyloid beta; AKT (PKB) – protein kinase B; CD – cluster of differentiation; CDK5 – cyclin dependent kinase 5; ERK – extracellular signal-regulated kinases; GFAP – glial fibrillary acidic protein; GluT3 – glucose transporter 3; GluT4- glucose transporter 4; GPCR – G-protein-coupled receptors; GSK3β – glycogen synthase kinase-3 beta; IFN – interferon; IL – interleukin; iNOS – Inducible nitric oxide synthase; IRF2 – interferon regulatory factor 2; JNK – c-Jun N-terminal kinase; LPS – lipopolysaccharides; MDA5 – melanoma differentiation-associated protein 5; MIP – macrophage inflammatory protein; mPGES-1 – microsomal prostaglandin E synthase-1; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; NGF – nerve growth factor; NLRP3 – nod-like-receptor family pyrin domain containing 3; NO – nitric oxide (II); nor-BNI – norbinaltorphimine; MAPK – mitogen-activated protein kinase; poly(I:C) – polyinosinic:polycytidylic acid; STAT3 – signal transducer and activator of transcription 3; PI3K – phosphoinositide 3-kinases; TLR3 – toll-like receptor 3; TLR4 – toll-like receptor 4; TNF-α – tumor necrosis factor alpha; TGF-β – transforming growth factor beta; ATP – adenosine triphosphate; ROS – reactive oxygen species; AD – Alzheimer's disease; PD – Parkinson's disease; GKS – glucocorticosteroids; BBB – blood-brain barrier; DNA – deoxyribonucleic acid; KOR – kappa opioid receptors; OPC – oligodendrocyte progenitor cell; OA – okadaic acid; ADEM – acute disseminated encephalomyelitis; RNA – ribonucleic acid; MS – multiple sclerosis; cAMP – cyclic adenosine monophosphate; TBI – traumatic brain injury; CNS – central nervous system; COX-2 – cyclooxygenase-2; EAE – experimental autoimmune encephalomyelitis.

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ОБЗОРЫ

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Подходы к изучению каппа-опиоидных лигандов на моделях нейровоспаления

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Разработка новых препаратов для коррекции нейровоспаления вызывает повышенный интерес, поскольку открывает возможности лечения широкого ряда заболеваний, включая болезнь Альцгеймера, болезнь Паркинсона, эпилепсию, шизофрению, депрессию и др. Каппа-опиоидные агонисты представляют собой перспективный класс соединений, обладающих высоким потенциалом применения при патологических состояниях, сопровождающихся развитием нейровоспаления.

Цель. Резюмировать информацию о текущих стратегиях, используемых для оценки нейротропных противовоспалительных эффектов каппа-опиоидных лигандов у лабораторных животных с индуцированным нейровоспалением.

Материалы и методы. В качестве средств поиска использовались поисковые системы и базы данных Google Scholar, PubMed, ScienceDirect, Scopus, e-Library. Поиск проводился по следующим ключевым словам и словосочетаниям: kappa opioids + neuroinflammation; kappa opioid receptors + neuroinflammation; neuroinflammation models; neuroinflammation models in rat; neuroinflammation models in mice, а также по их русскоязычным аналогам. Были найдены 148 релевантных статей, из которых 122 были включены в настоящий обзор.

Результаты. В настоящем обзоре были рассмотрены различные экспериментальные модели нейровоспаления, индуцированного химическими агентами и бактериальным эндотоксином, а также травматические и генетические модели на мышах и крысах. Кроме того, были критически оценены сильные стороны и ограничения каждой модели для определения наиболее подходящей стратегии исследования взаимосвязей между нейровоспалением и сигнальными путями каппа-опиоидной рецепторной системы.

Заключение. Рассмотрены особенности нейротропной противовоспалительной активности каппа-опиоидных лигандов. В обзоре обсуждаются как экспериментальные модели, в которых изучались эффекты агонистов каппа-опиоидных рецепторов, так и модели, в которых противовоспалительные свойства агонистов каппа-опиоидов еще не изучены.

Ключевые слова: нейровоспаление; экспериментальная фармакология; экспериментальные модели; нейроиммунные процессы; микроглия; каппа-опиоидные рецепторы; каппа-опиоидные агонисты; липополисахарид

Список сокращений: Aβ – бета-амилоид; AKT (PKB) – протеинкиназа B; CD – кластер дифференцировки; CDK5 – циклинзависимая киназа 5; ERK – киназы, регулируемые внеклеточными сигналами; GFAP – глиальный фибриллярный кислый белок; GluT3 – глюкозный транспортер тип 3; GluT4 – глюкозный транспортер тип 4; GPCR – рецепторы, сопряженные с G-белком; GSK3β – киназа гликогенсинтазы-3 бета; IFN – интерферон; IL – интерлейкин; iNOS – индуцибельная синтаза оксида азота; IRF2 – регуляторный фактор интерферона 2; JNK – c-Jun N-концевая киназа; LPS – липополисахарид; MDA5 – белок, ассоциированный с дифференцировкой меланомы 5; MIP – воспалительный белок макрофагов; mPGES-1 – микросомальная простагландин E-синтаза-1; NF-κB – ядерный фактор каппа-би; NGF – фактор роста нервов; NLRP3 – белок семейства Nod-подобных рецепторов с пириновым доменом 3; NO – оксид азота (II); nor-BNI – норбиналторфимин; APK – митоген-активируемая протеинкиназа; poly(I:C) – полиинозиновая-полицитидиловая кислота; STAT3 – сигнальный белок и активатор транскрипции 3; PI3K – фосфоинозитид-3-киназы; TLR3 – толл-подобный рецептор 3; TLR4 – толл-подобный рецептор 4; TNF-α – фактор некроза опухоли-альфа; TGF-β – трансформирующий фактор роста бета; АТФ – аденозинтрифосфат; АФК – активные формы кислорода; БА – болезнь Альцгеймера; БП – болезнь Паркинсона; ГКС – глюкокортикостероиды; ГЭБ – гематоэнцефалический барьер; ДНК – дезоксирибонуклеиновая кислота; КОР – каппа-опиоидные рецепторы; КПО – клетка-предшественник олигодендроцитов; ОК – окадаевая кислота; ОРЭМ – острый рассеянный энцефаломиелит; РНК – рибонуклеиновая кислота; РС – рассеянный склероз; цАМФ – циклический аденозинмонофосфат; ЧМТ – черепно-мозговая травма; ЦНС – центральная нервная система; ЦОГ-2 – циклооксигеназа 2; ЭАЭ – экспериментальный аутоиммунный энцефаломиелит.

INTRODUCTION

Neuroinflammation is defined as a common reaction in the brain and spinal cord that occurs in response to various provoking factors, such as infectious agents, a traumatic brain injury, a stroke, exposure to toxins, and others. While an inflammation is a necessary component of the recovery process after a traumatic injury, it can become pathological due to dysregulation of the immune response [1].

Neuroinflammation is a complex process that involves biochemical, histological, and systemic changes [2]. It is characterized by the production of cytokines,

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chemokines, and reactive oxygen species (ROS) by astrocytes and microglia, leading to an increased blood-brain barrier permeability, an immune cell infiltration into the nervous tissue, cerebral edema, and neuronal cell death. The clinical features of acute neuroinflammation are diverse and vary depending on the location of the affected tissue, but typically include chronic neuropathic pain [3], cognitive deficits, and apathy [4].

The primary role in the development of neuroinflammation is attributed to microglia cells, which are resident macrophages of the brain. In normal conditions, microglia cells participate in the synaptic function, cell apoptosis, and a neuronal activity. There are two primary phenotypes of microglia cells in the nervous system, M_1 and M_2. M_1, or pro-inflammatory microglia, produces pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), STAT3, IL-6, IL-12, IL-23, and ROS. In contrast, M_2 mediates anti-inflammatory and reparative processes by releasing IL-10, IL-4, IL-13, and transforming growth factor beta (TGF-β) [5].

Neuroinflammation is not only driven by microglia-produced pro-inflammatory mediators, but is also associated with the migration of B-lymphocytes, which release antibodies that target the myelin sheath and promote demyelination of the nervous tissue [6]. Additionally, cytokines can cross the blood-brain barrier from the systemic circulation, linking peripheral and central immune responses [7].

From a clinical perspective, neuroinflammation is a critical pathological component of various neuropsychiatric and neurodegenerative diseases. It significantly contributes to the development of neuropsychiatric conditions such as schizophrenia, multiple sclerosis, and Alzheimer's disease (AD) [8]. In AD, the aggregation of β-amyloid in the intercellular space leads to the formation of senile plaques and neurofibrillary tangles, which activate pro-inflammatory microglia [9]. In the postmortem analysis of patients with Alzheimer's disease (AD), as well as in experimental AD models, morphological changes are detected that indicate a microglial activation and inflammation in the tissues surrounding amyloid plaques.

In Parkinson's disease (PD), which is characterized by the degeneration of dopaminergic neurons in the substantia nigra and the presence of aggregated α-synuclein in Lewy bodies, there is evidence of a microglial activation and the release of pro-inflammatory cytokines. An increase in the concentration of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as the activation of their corresponding receptors, has been observed [10].

The involvement of the immune system in psychiatric diseases has been well established through a large body of research. There are genetic associations between a major depressive disorder, a dysregulation of several immune cascades, and cytokine imbalances [11-13]. Patients with chronic inflammatory diseases, such as autoimmune diseases, have an increased risk of a developing depression. This risk is due not only to the psychological burden of the disease itself but also to the elevated levels of pro-inflammatory cytokines [14].

In the literature, there is evidence for increased risk of depression following immunotherapy, but the exact mechanism underlying this phenomenon is not fully understood. The administration of pro-inflammatory cytokines has been shown to induce a depressive-like state in the animal models, and depression is a common side effect of the interferon treatment [15]. In other cases, it is believed that peripheral immune cells and cytokines can cross the blood-brain barrier and impact the primary neurotransmitter systems involved in the pathogenesis of depression, including monoaminergic, glutamatergic, and GABAergic transmission [16].

Neuroinflammation also plays a role in epilepsy. Epileptogenesis is believed to result in the damage to the CNS tissue, creating foci of inflammation characterized by a predominance of the pro-inflammatory phenotype of microglia. This phenotype is characterized by an increased gene expression of various proteins, including inducible nitric oxide synthase and CD16/32 antibodies, as well as an increase in the release of certain inflammatory factors such as IL-1β, IL-6, and TNF-α [17].

Currently, the treatment of neuroinflammatory-associated CNS diseases with available pharmacological agents has been largely unsuccessful due to the limited efficacy or adverse side effects. Conventional therapy typically involves non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids (GCS), and other immunosuppressants [18].

Although the prior research has demonstrated the effectiveness of NSAIDs in managing various neurodegenerative processes, their usage has not been recommended yet due to the potential harm and lack of efficacy in treating or preventing dementia and cognitive decline. Despite a high efficiency in suppressing neuroinflammatory processes, a prolonged usage of corticosteroids is accompanied by various side effects, including mood disorders, gastrointestinal problems, headaches, and an increased risk of osteoporosis, diabetes, and infectious diseases.

Hence, the investigation of new preventive and therapeutic agents that target neuroinflammation is critical. The class of kappa agonists appears to be a promising option that can significantly decrease neuroinflammatory processes and mitigate the severity of associated diseases [19].

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THE AIM of the study was to provide a summary of the current strategies employed to evaluate the neurotropic anti-inflammatory effects of kappa-opioid ligands in laboratory animals with induced neuroinflammation.

MATERIALS AND METHODS

The databases, such as Google Scholar, PubMed, ScienceDirect, Scopus, e-Library were used as search tools. The search comprised the relevant keywords and phrases shown in Fig. 1. The preference was given to the studies that used rats and mice as experimental animals, owing to the widespread availability and thorough knowledge of their metabolic characteristics.

A total of 148 articles published between 1975 and 2022 were initially identified. After an initial screening of the titles and abstracts, 26 duplicate and irrelevant articles were excluded, as their design did not include descriptions of aspects or patterns of the neuroinflammation process, the effects of kappa-opioid receptors, and the experimental animal models applicable to modeling the similar pathological conditions. A total of 122 publications were included in the review.

RESULTS AND DISCUSSION

1. General characteristics of kappa-opioid receptors

Opioid receptors are members of the G protein-coupled receptor family and are predominantly distributed in the nervous system. There are four main subtypes of opioid receptors: delta (δ), kappa (κ), mu (μ), and nociceptive receptors [20]. Opioid receptors play a significant role in mediating various pharmacological effects, including analgesia [21], sedation [22], anticonvulsant [23], neuroprotection, and some others [24]. The recent evidence has established that kappa-opioid receptors are also present on immune cells [25], and their activation leads to the secretion inhibition of IL-6, TNF-α, and IL-1β. This mechanism contributes to the attenuation of immune responses [26].

Upon the activation, G protein-coupled receptors, including kappa-opioid receptors, trigger a cascade of intracellular signaling pathways. Specifically, the receptor causes the α subunit of the G-protein to dissociate from the β and γ subunits, and these subunits subsequently affect downstream intracellular signaling proteins or target functional proteins. $G\alpha_i$ inhibits adenylate cyclase, which is involved in the synthesis of cAMP, and activates potassium channels in the postsynaptic neuron. At the same time, $G\beta_\gamma$ causes the closure of voltage-gated calcium channels in the presynaptic neuron. Overall, this process results in a reduction of the neuron's responsiveness to excitatory neurotransmitters and a decrease in their secretion [27].

A number of kappa-opioid agonists can exhibit biased agonism [28], which is considered as a ligand-dependent selectivity for certain signal transduction pathways relative to a reference ligand at the same receptor. When the kappa receptor is activated, two intracellular pathways are involved: adenylate cyclase mediated and β-arrestin mediated. The second pathway leads to the phosphorylation and activation of the mitogen-activated protein kinase p38 (p38 MAPK) and its activation, causing the translocation of the SERT gene and dysphoria.

The activation of p-STAT3 and suppression of caspase-3 are among the mechanisms through which kappa-opioid receptor (KOR) agonists can modulate neurodegeneration and neuroinflammation [29, 30]. KOR agonists may also reduce glutamate excitotoxicity by inhibiting the level of free Ca^{2+} in synaptosomes and the release of presynaptic glutamate by closing N-type Ca^{2+} channels [31-33].

KOR agonists have been reported to have a positive effect on remyelination and oligodendrocyte maturation in autoimmune diseases, in addition to their anti-inflammatory properties. This effect is believed to be due to the activation of the GPCR kinase, the MAPK family (ERK 1/2, p38, and JNK), as well as the JAK2/STAT3 and IRF2 cascade [27]. The ERK 1/2 and JAK2/STAT3 pathways seem to be the most promising in terms of both clinical efficacy and safety. Oligodendrocyte progenitor cells (OPCs) increase a pSTAT3 expression in the areas of enhanced oligodendrogenesis after the nerve tissue injury, while the deletion of STAT3 in OPCs reduces the oligodendrocyte differentiation during the cell growth and development [31]. Thus, STAT3 phosphorylation in the oligodendrocyte lineage cells may be one way in which KOR agonists mediate their promyelinating effects in synergy with ERK1/2 signaling [34].

2. Mechanisms of neuroinflammation in different experimental models

2.1. Models based on immune response

2.1.1 LPS-induced neuroinflammation

This is one of the most widely used models suitable for both *in vivo* and *in vitro* studies. The administration of lipopolysaccharide (LPS) results in the formation of the LPS-CD14 complex, which activates microglia and causes the release of pro-inflammatory mediators: cytokines, chemokines, and proteins of the complement system. The manifestations of the LPS-induced inflammation can differ considerably depending on various factors such as

the mode and duration of the administration, as well as the age of the animals under study.

Microglia cells play a key role in the pathogenesis of neuroinflammation. Microglia can polarize into M_1 (a pro-inflammatory phenotype) or M_2 (an anti-inflammatory phenotype) after the activation. The M_1 phenotype is associated with the production of pro-inflammatory cytokines, which can lead to the nerve cells damage, astrocyte apoptosis, and the blood-brain barrier disruption, while the M_2 phenotype exerts the opposite effect [35].

The relationship between the LPS-induced neuroinflammation and the kappa opioid receptor system has been well studied. LPS has been observed to decrease the expression of KOR. It is hypothesized that the reduction in the KOR function triggers the activation of microglia, leading to the production of pro-inflammatory cytokines within the brain [36].

Dynorphins, the main KOR ligands, are known to induce the M_2 polarization of microglia *via* the suppression of the TLR4/NF-κB pathway. This effect has been demonstrated in the LPS-stimulated BV-2 microglial cells. Conversely, the treatment with the KOR inhibitor GNTI resulted in an opposing effect [19].

It is noteworthy that the administration of dynorphin-A (an endogenous KOR agonist) led to the inhibition of the LPS-induced CD16/32 expression and the suppression of M_1 cytokine production, including IL-1β and IL-6. A comparable outcome following the treatment with the selective kappa agonist U50,488 was observed, and the effect was attenuated by the KOR antagonist nor-binaltorphimine (nor-BNI) [37]. Moreover, dynorphin-A increased the CD206 expression and stimulated the production of M_2-associated cytokines (IL-4 and IL-10) in the LPS-stimulated BV-2 cells. In contrast to dynorphin-A, the selective kappa-opioid receptor antagonist GNTI produced opposing effects and prevented dynorphin-A-mediated polarization of BV-2 microglia into the M_2 phenotype [19].

In the central nervous system, microglia cells are distributed unevenly [38], with the highest expression of the mRNA encoding KOR found in the striatal region [39]. Further research is needed to investigate whether there are regional differences in the response of microglia to the stimulation or blockade of KOR. The role of microglial kappa-opioid receptors in the regulation of neuroinflammation remains unclear, as the influence of circulating pro-inflammatory cytokines released by other immune cells also plays a role [36]. It is important to consider the age and sex of the individuals exposed to LPS, since the administration of LPS at an early age can provoke (depending on sex) different responses in behavior and relative expression levels of pro- and anti-inflammatory factors [40, 41]. It has been reported that in the young rats, in contrast to more mature ones, the level of IL-1β increased to a greater extent during the development of neuroinflammation, but the level of interferon-γ increased to a lesser extent [42].

It has been demonstrated that LPS increases the levels of TNF-α and IL-1β by interacting with Toll-like receptor 4 (TLR4) [43]. TNF-α and IL-1β levels are regulated by a nuclear factor κB (NF-κB). Although these cytokines are essential components of the innate immune response, their excessive expression can lead to endotoxemia. The studies have shown that the kappa-opioid agonists U50,488 and salvinorin A reduce the levels of TNF-α and IL-10 (but not IL-1β) in the LPS-stimulated peritoneal macrophages [44, 45].

In summary, despite the significant insights gained from the current model, further investigation is required to uncover the complete network of interactions between the KOR and the neuroinflammation pathways induced by LPS.

2.1.2. Neuroinflammation induced by polyriboinosinic polyribocytidylic acid

Polyinosinic-polycytidylic acid (poly(I:C) is a synthetic analogue of double-stranded RNA that, when administered to experimental animals, triggers systemic inflammation, ultimately leading to the development of neuroinflammation [46].

Based on this, a model wherein a single intravenous injection of poly(I:C) was proposed. It is given to pregnant female rats on the 17 days of gestation (GD17). The exposure of the mouse offspring to a systemic immune challenge during a specific time window in late gestation (GD17) increases their susceptibility to the age-related brain pathology and cognitive impairment [47].

In this case, the mechanism of neuroinflammation is mediated by the TLR3-induced microglial activation [48], followed by the NF-kB-dependent induction of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, TNF-α, and types I and II interferons [49]. In turn, kappa-opioid agonists are able to suppress the development of inflammation by reducing the level of these cytokines, primarily IL-1α, IL-1β, IL-2, and IL-17 [50].

It is reported that poly(I:C) enhances the synthesis of the enzymes associated with the prostaglandin E2 production through the activation of various microglial signaling pathways. In addition, TLR4-associated signaling, which plays an important role in the synthesis of COX-2 and mPGES-1, is also enhanced. Thus, it is proposed that these two TLR3 mechanisms independently mediate the neuropathological effects of poly(I:C) [51, 52].

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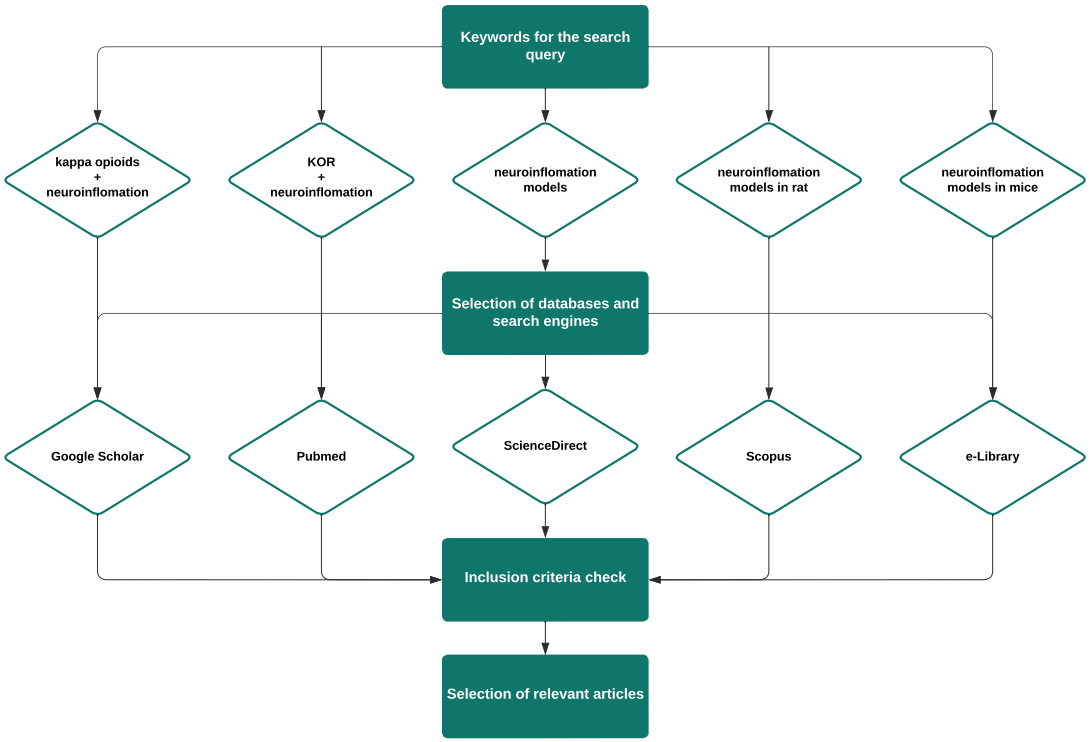

Figure 1 – Flowchart describing methodology for searching and processing literature data

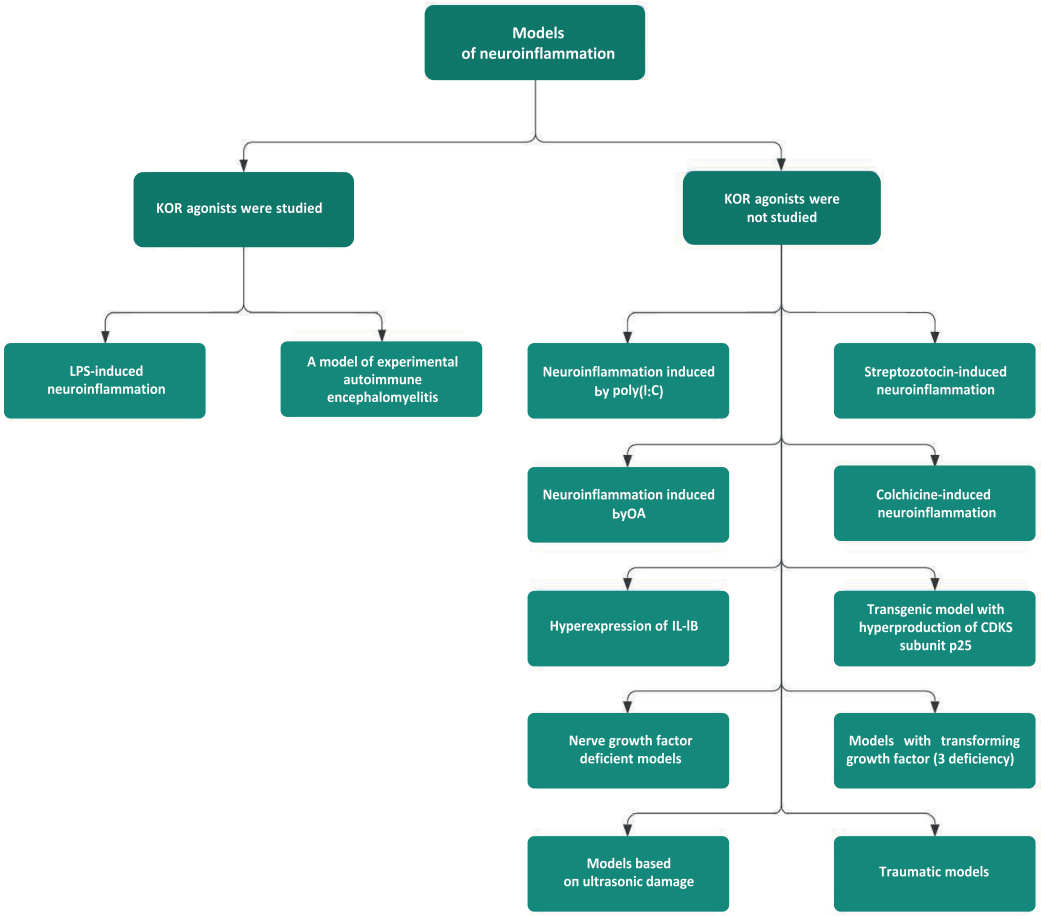

Figure 2 – Experimental models of neuroinflammation for assessing the efficacy of kappa-opioid receptor agonists

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Poly(I:C) can engage other mechanisms. In the mice with an inactivated MDA5 gene (MDA5$^{-/-}$) the administration of poly(I:C) did not result in an elevation of serum IFN-γ levels compared to wild-type mice. The production of IL-6 and IL-12p40 was also impaired in MDA5$^{-/-}$ mice [51]. Moreover, poly(I:C) can also trigger the formation of NLRP3 inflammasomes *via* TLR3- and MDA5-independent pathways [54]. At the same time, the recent studies have shown that the NLRP3-mediated neuroinflammation is closely associated with the secondary brain damage after intracerebral hemorrhage [55].

Poly(I:C) activates MAPKs, which are important regulators of the expression of the inflammatory mediators [52]. For example, the activation of ERK promotes an increase in the production of nitric oxide and IL-1β in macrophages [56].

2.1.3. Model of experimental autoimmune encephalomyelitis

The experimental autoimmune encephalomyelitis (EAE) model is mainly used as an animal model of autoimmune inflammatory diseases of the CNS, usually in the studies of multiple sclerosis (MS). This model is instrumental in studying the pathogenesis of MS and evaluating new therapeutic interventions for its prevention and treatment. Additionally, certain variations of the EAE model can reproduce other, less prevalent CNS inflammatory diseases like monophasic acute disseminated encephalomyelitis (ADEM) or optomyelitis (Devic's disease).

The EAE consists of two phases: the induction phase and the effector phase. The induction phase involves the priming of myelin epitope-specific CD4$^+$ T cells by the myelin or myelin antigen injection. During the effector phase, these activated myelin-specific T cells migrate into the CNS and produce chemokines and cytokines that trigger an influx of peripheral mononuclear phagocytes into the CNS. The cytokines produced by T cells also activate peripheral monocytes and CNS-resident microglial cells. This activation leads to the axonal demyelination, the process mediated by the phagocytic activity of the activated mononuclear cells, along with the inflammatory and cytotoxic effects of cytokines such as IFN-γ, TNF-β, IL-17, TNF-α, and NO, which are released from the activated CD4$^+$ T cells and monocytes [57]. Typically, between 7 to 12 days following immunization, the inflammatory cells infiltrate the CNS and cause the destruction of the myelin sheath, leading to the movement impairments and a gradual onset of the hind limb paralysis [58]. A passive or adoptive-transfer EAE (AT-EAE) can be induced in the recipient animals by transfer of the pathogenic myelin-specific CD4$^+$ T cells that were generated in the donor animals *via* an active immunization. This process involves only the effector phase of the immune response [59].

The previous studies suggest that the activation of KOR prevents the progression of multiple sclerosis. For example, the administration of nalfurafine and U50,488 contributed to the restoration and remyelination of the nervous tissue after EAE. This effect was blocked by the KOR antagonist nor-BNI, indicating that nalfurafine mediates the recovery from EAE in a KOR-dependent fashion [2]. In addition, the administration of nalfurafine resulted in a reduction of the CNS infiltration with the CD4$^+$ and CD8$^+$ T cells, and also improved the immune homeostasis by suppressing Th17 responses [2].

2.2 Neurotoxic models

2.2.1 Streptozotocin-induced neuroinflammation

Streptozotocin is currently the most basically used agent in the diabetes mellitus research [60]. As the molecule is unable to cross the blood-brain barrier, its systemic administration does not result in a direct impact on the brain cells [61]. Nonetheless, several studies have suggested that laboratory animals with diabetes mellitus develop neuronal degeneration in the frontal lobes and hippocampal atrophy [62]. It is believed that these effects are linked to the pathological mechanisms such as an oxidative stress, which arises from the production of hydrogen peroxide and nitric oxide, as well as the DNA damage. [63, 64].

Neuroinflammation is induced by an intravenous or intracerebroventricular streptozotocin injection. The intracerebroventricular administration of streptozotocin (1–3 mg/kg) provokes neurodegenerative symptoms that resemble those found in Alzheimer's disease (AD) [65].

The manifestation of neurodegeneration following a streptozotocin injection can vary between 1-6 weeks depending on the laboratory animal species and their unique traits [66, 67]. It should be emphasized that in this model not only neuroinflammation but also other manifestations of AD are observed.

Several authors believe that a decreased PI3K/AKT signaling activity and the intraneuronal glucose metabolism are key mechanisms for the development of AD, both in natural conditions and in the experimental model [68]. The studies on epilepsy have demonstrated that dynorphin acting on the KOR can engage the PI3K/AKT pathway, leading to neuroprotection [69].

In the periphery, the insulin's primary role is to lower a blood glucose concentration *via* GluT4. Although GluT4 is mostly found in the adipose and muscle tissues, it has also been discovered in the hippocampus. Researchers

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suggest that under the conditions of the increased energy demand, GluT4 can transfer glucose to the brain cells, performing an auxiliary function along with GluT3, the main neuronal transporter. GluT4 plays an important role in memory processes, and therefore, a decrease in the activity of this transporter may underlie cognitive impairments associated with the insulin resistance [70]. The kappa-opioid receptor agonists can reduce diabetes mellitus symptoms (including neuroinflammatory processes caused by diabetes mellitus) through the GluT4 translocation and adiponectin phosphorylation, including neuroinflammatory processes caused by diabetes mellitus [71].

The neuroprotective effect of kappa-opioid agonists is linked to the reduction of the ROS production and an oxidative stress, a key component of neuroinflammation in the streptozotocin-induced model [72]. However, at least one study found out that KOR agonists can stimulate the ROS production by activating JNK. It remains unclear how the KOR-mediated ROS production contributes to neurotoxicity [73].

2.2.2 Neuroinflammation induced by okadaic acid

Okadaic acid (OA) selectively inhibits the activity of protein phosphatase 2A [74], which is one of the factors involved in the pathogenesis of AD and has been linked to neuroinflammatory diseases [75]. A neurotoxic effect of OA includes hyperphosphorylation of the tau protein, cell apoptosis, beta-amyloid deposition, an oxidative stress, neuroinflammation [76-78], which are accompanied by cognitive impairments, in particular, memory disorders [79, 80].

Some publications [81, 82] point out to the fact that the drugs designed to treat dementia may be also effective in treating the symptoms caused by the administration of OA. This makes it possible to suppose that neuroinflammation is the secondary consequence of neurodegeneration. In this regard, an experimental model involving the intrahippocampal administration of OA was proposed to induce an oxidative stress [79].

The studies found out that the kappa-opioid agonist U50,488H reduces serum levels of TNF-α, IL-1β and IL-6, suppresses the expression of NF-κB in the hippocampus, and decreases the rate of apoptosis of hippocampal neurons in the rats, indicating its effectiveness in combating an oxidative stress and neuroinflammation [83]. These cytokines can be used as markers when studying kappa-opioid ligands in the model of neuroinflammation induced by OA.

2.2.3 Colchicine-induced neuroinflammation

Colchicine is a known cytotoxic agent that disrupts the axoplasmic transport, leading to the neuronal death [84]. Recent investigations have revealed that a systemic administration of colchicine can elevate the concentration of COX-2 in the cytoplasm of cells [85], thereby inducing neuroinflammation and specific cognitive and behavioral symptoms [82].

In the model of colchicine-induced neuroinflammation, KORs can mediate neuroprotective effects by reducing the excessive production of iNOS, COX-2, TNF-α, and IL-1β, as demonstrated in the study of the LPS-induced inflammation in alveolar macrophages [86]. Furthermore, KORs have been found out to impact an oxidative stress. For instance, the endogenous KOR agonist dynorphin-A has been shown to decrease an oxidative stress during epileptiform discharges in hippocampus [69].

2.3. Genetically determined models

2.3.1. Hyperexpression of IL-1ß

Neuroinflammation is characterized by an increased production of IL-1β [87]. This led to the creation of a transgenic mouse line overexpressing interleukin-1β [88]. The elevated levels of IL-1β lead to the development of microgliosis, astrogliosis, and a chronic increase in pro-inflammatory agents. However, this model shows no significant change in the synthesis of the beta-amyloid precursor protein, and the number of amyloid plaques may even decrease, setting it apart from other models [89]. Furthermore, despite significant cognitive impairments, neuronal apoptosis is not histologically detected in this model [90]. Therefore, this model can be used to reproduce neuroinflammation without neurodegenerative changes.

Kappa-opioid receptor agonists may act in this model by reducing the levels of IL-1α, IL-1β, IL-2, and IL-17 [91] and inhibiting the Nod-like receptor of the NALP family (NLRP3), thus suppressing the inflammatory process.

2.3.2. Transgenic model with hyperproduction of cyclin-dependent kinase 5 (CDK5) subunit p25

Based on the available literature data, the changes in the expression of some cell cycle proteins can serve as a biomarker and a cause of neuroinflammatory processes. Cyclins and cyclin-dependent kinases, such as CDK5, have received a particular attention [92]. Normally, the p35 subunit forms a complex with CDK5 and regulates corticogenesis, a synaptic vesicle metabolism, a neurotransmitter release, and a signal transduction in brain cells [93]. However, under neurotoxic conditions, an aincreased cleavage of p35 into p25 by calcium-dependent kinase leads to the CDK5 dysregulation and neurotoxic effects [94, 95].

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Similar phenomena have been observed in patients with neurodegenerative diseases [92], and it is believed that the p25-CDK5 complex induces hyperphosphorylation of the tau protein [96]. In the animal models, this reaction develops in response to neuroinflammation, which is characterized by astrocytosis and elevated levels of pro-inflammatory cytokines, including TNF-α, IL-1β, and MIP-1α [97].

In mice, the pathological changes sequentially appear in the order as below: the onset of neuroinflammation (at the end of the 1st week), hyperphosphorylation of the tau protein (at the 5th week), cognitive deficits (at the 7th week), and finally, accumulation of amyloid plaques (at the 9th week) [98, 99].

2.3.3 Nerve growth factor deficient models

This model is based on the use of transgenic laboratory animals that express antibodies against a nerve growth factor (NGF). In such animals, the development of neurodegenerative processes is evident, which is characterized by visual recognition and spatial memory deficits, neuronal degeneration, cholinergic insufficiency, hyperphosphorylation of the tau protein, and the formation of β-amyloid plaques [100, 101]. At the biochemical level, the expression of various pro-inflammatory cytokines, such as IL-1β, TNF-α, and IFN-γ-induced ATPase, is also observed, which occurs due to the development of an autoimmune reaction [102].

Agonists of KOR can attenuate the progression of this process *via* the inhibition of the TLR4-dependent signaling pathway in neurons of the peripheral nervous system, resulting in the reduced production of pro-inflammatory interleukins and an immunosuppressive effect [103].

2.3.4. Models with transforming growth factor β deficiency

A transforming growth factor-β (TGF-β) is a cytokine involved in various parts of the inflammatory process. Its effects depend on the type of the target cells, the cellular environment, as well as the degree and duration of exposure [104]. In the CNS, TGF-β is produced by both neurons and glial cells [105]. In particular, TGF-β1 has a protective effect in neuropathies by preventing the glia activation, reducing the release of pro-inflammatory cytokines, and reducing the infiltration of T-lymphocytes and macrophages into the peripheral nervous system. A moderate upregulation of the TGF-β1 synthesis in astroglia increased Aβ clearance in the old transgenic mice expressing a human β-amyloid precursor protein gene [106], thereby confirming a neuroprotective role of TGF-β. On the contrary, in the laboratory animals with the TGF-β gene knockout, the neuroprotective effects are completely absent and a pronounced neurodegeneration is detected [107].

Nevertheless, upon the examination of autopsy samples taken from the patients with AD, an elevated level of TGF-β was discovered in cerebral vessels, which might contribute to the release of pro-inflammatory cytokines such as TNF-β and IL-1β, from the brain endothelial cells [108]. This finding is consistent with the experimental data obtained from the transgenic mice in which a prolonged overexpression of TGF-β correlates with an increased perivascular amyloidogenesis [109]. As a result, these data raise questions about a neuroprotective role of TGF-β and the representativeness of the model.

2.4 Physical models

2.4.1. Models based on ultrasonic damage

The aforementioned animal models affect the whole body systemically, involving various organs and tissues in the pathological process, including those outside the nervous system. To achieve an isolated effect on the brain, Kovacs ZI et al. proposed a technique based on focused ultrasonic pulses [110]. The exposure to a high-frequency sound led to an acoustic cavitation and a sterile damage to the BBB with the development of an inflammatory reaction in the brain parenchyma. This was confirmed biochemically by an increase in the levels of the heat shock protein 70, IL-1, IL-18, TNFα, and the expression of pAKT and pGSK3β. However, the activation of other signaling pathways such as p38-MAPK, pERK, and pJNK, has not been confirmed.

This approach has been proposed for the treatment of tumor diseases [111] and as a method that facilitates a drug penetration through the BBB [112]. Nevertheless, it is reasonable to speculate that the localized neuroinflammation resulting from the BBB damage could serve as a valuable tool for investigating the properties of putative neuroprotective drugs, such as KOR.

2.4.2. Traumatic models

An alternative form of a physical impact on the brain is through a mechanical damage or traumatic brain injury (TBI). Neuroinflammation is initiated during the acute phase of TBI and persists throughout the chronic phase [113]. It is important to note that inflammation can take place during the recovery process after TBI, which often leads to the development of secondary undesirable effects associated with hyperproduction of pro-inflammatory cytokines [114].

TBI results in the activation of glial cells, a release of pro-inflammatory mediators, and a recruitment of leukocytes (migration of peripheral immune cells to the

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affected area is accelerated) [115, 116]. The activation of microglia causes an imbalance between M_1 and M_2 phenotypes [117], leading to the increased cytotoxicity and long-term neurodegenerative processes.

In addition to TBI, neuroinflammation can develop as a result of other injuries. For example, a model of a tibial fracture in rats was proposed [118]. The study indicates that such an injury leads to an increase in the level of IL-1β and a marker of astrogliosis GFAP, as well as microglial and astrocytic responses in the hippocampus. However, the exact mechanism underlying this phenomenon remains unclear.

The earlier studies have also established a relationship between a tibial fracture and the severity of the consequences of a TBI [119]. The authors observed more pronounced neuroinflammation and cerebral edema in the animals exposed to combined traumatic effects. It is hypothesized that a hyperproduction of inflammatory mediators in the brain may be linked to the development of systemic inflammation that occurs as a result of fractures of large bones [120], resulting in more severe consequences of TBI.

Taking into account the fact that TBI-induced inflammation occurs through typical signaling pathways it can be assumed that KOR agonists could have a significant neuroprotective effect. A KOR activation suppresses the production of pro-inflammatory cytokines IL-1β and IL-6, resulting in a shift towards the neuroprotective M_2 phenotype. Given a high incidence of TBI both in Russia [121] and worldwide [122], the evaluation of the therapeutic potential of kappa-opioid agonists in this model appears to be particularly promising.

CONCLUSION

Neuroinflammatory processes in the brain are associated with an increase in the density of immunoreactive microglia, dystrophic, apoptotic and necrotic changes in oligodendroglia, demyelination and degeneration of axons, and an imbalance of cytokines. Given the difficulties in treating neuroinflammation-related diseases, there is a need to search for and develop new drugs.

To date, numerous studies indicate protective effects of kappa-opioid agonists in neuroinflammation-related diseases. Several mechanisms may be involved in these effects, including a direct influence on neurons, glia (especially microglia), and cells of the immune system (both within and outside of the CNS). However, the clinical potential of using kappa-opioid agonists for the conditions associated with neuroinflammation has not been fully explored.

The model of neuroinflammation induced by LPS is the most extensively studied, particularly regarding the investigation of the anti-inflammatory effects of KOR agonists. Transgenic and knockout models, as well as various physical and traumatic models are currently actively used, however, their representativeness (the ability to most fully and adequately reproduce a specific pathology) may be questionable due to their reductionistic nature and limitations, since neuroinflammation is characterized by extremely complex pathogenesis and etiology (Fig. 2).

There are a number of models where the activity of KOR ligands has not been previously evaluated, which opens up a pool of opportunities for exploration of the anti-inflammatory properties of this class of compounds.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Konstantin Yu. Kalitin – tasks setting, concept development, scientific and methodical literature analysis, article writing and editing; Alexander A. Spasov – draft manuscript critical revision, making intellectual comments, final manuscript approval; Olga Yu. Mukha – data collection, manuscript drafting and writing, text editing and formatting.

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