REVIEW

δ-Opioid receptor as a potential therapeutic target for ischemic stroke

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Abstract

Ischemic stroke is a global epidemic condition due to an inadequate supply of blood and oxygen to a specific area of brain either by arterial blockage or by narrowing of blood vessels. Despite having advancement in the use of thrombolytic and clot removal medicine, significant numbers of stroke patients are still left out without option for treatment. In this review, we summarize recent research work on the activation of δ-opioid receptor as a strategy for treating ischemic stroke-caused neuronal injury. Moreover, as activation of δ-opioid receptor by a non-peptidic δ-opioid receptor agonist also modulates the expression, maturation and processing of amyloid precursor protein and β-secretase activity, the potential role of these effects on ischemic stroke caused dementia or Alzheimer's disease are also discussed.

Key Words: *agonist; AKT; amyloid precursor protein; BDNF; ischemic stroke; neuroprotection; δ-opioid receptor; p38 MAPK; PI3K; TrkB*

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Introduction

Stroke is associated with long-term neurological inability and mortality condition worldwide (Pendlebury and Rothwell, 2009; Tschirret et al., 2018) which is either commonly due to vascular occlusion (ischemic stroke) or rupture (hemorrhagic stroke) (Ojaghihaghighi et al., 2017). Among stroke, ischemic stroke is the most common that accounts for 87% of total strokes cases in many of the Western countries (Musuka et al., 2015; Ramiro et al., 2018). Ischemic stroke commonly arises due to an interruption of blood supply in an area of brain after having narrowing or occlusion condition in blood vessels (O'Donnell et al., 2016). To provide care and treatment for this disease condition in patients, removal of blood clot and correction of damaged area in blood vessel along with rehabilitation of patients are the major significant adapted approaches used till today (Moussaddy et al., 2018). Despite having a lot of progress in research to explore thrombolytic agents for ischemic stroke, tissue plasminogen activator is the only drug approved by the U.S. Food & Drug Administration for its treatment (Liang et al., 2014). The tissue plasminogen activator is a serine protease involved in the breakdown of blot clots and improving blood flow if administered within less than 4.5 hours after the onset of stroke symptoms (Marshall, 2015). Despite of its significant therapeutic role, tissue plasminogen activator has limited use due to its narrow therapeutic window, selective efficacy, and hemorrhagic complication (Liu et al., 2018). Therefore, alternative therapeutic agents to treat ischemic stroke are needed to extend treatment availability and to promote brain repair leading to neurological recover.

Opioid receptors are G protein coupled receptors, widely distributed in nervous system and classified into 3 major types: δ-, μ- and κ-opioid receptors (Grant Liska et al., 2018). Both μ- and κ-opioid receptors mediate analgesic properties of opiates, but activation of the latter also produces side effects including dysphoria, hallucinations, and dissociation, which has limited their clinical usefulness (Zhou et al., 2013). Unlike μ- and κ-opioid receptors, the exact role of δ-opioid receptor (DOR) in modulating pain relief remains for debate but it is accepted that activation of DOR is beneficial for the treatment of chronic pain. Additionally, activation of DOR does not induce μ opioid-like side effects such as dependence, respiratory depression and constipation. More interestingly, mounting data suggest that activation of DOR with some synthetic small molecule agonists enhances neuronal survival and reduces cell death in some neurological disease conditions (Crowley et al., 2017; Lee et al., 2018). Here, we review recent developments related to DOR as a therapeutic target for treating ischemic stroke and summarize some potential mechanisms underlying DOR mediated neuroprotection. An electronic search of the Pubmed for literature describing the role of activation of DOR in either cerebral ischemia or ischemic stroke was performed using the following terms: delta opioid receptor AND agonist AND cerebral ishcemia (or hypoxia or ischemic stroke). The search results were further examined by checking their titles and abstracts to including studies only using neuronal cultures, rats, mice and non-human primates.

δ-Opioid Receptor Agonists

DOR, similar to the other two types of opioid receptors, is a seven-transmembrane protein and belongs to the G-protein-coupled receptor (Gendron et al., 2016). Along with studies of the functions of DOR, a number of endogenous and exogenous agonists that activate DOR, as well as antagonists that inhibit DOR activity are utilized (Zhao et al., 2006; Wang et al., 2011, 2016; Fang et al., 2013; Tian et al., 2013). These agonists are either peptide ligands (such as

Leu-enkephalin) or non-peptide small molecules and they play a neuroprotective role in ischemic stroke. Among the non-peptidic DOR agonists, BW373U86 was the first developed, although it induced convulsions in mice (Chang et al., 1993). After one year, an analog of the compound, termed as SNC80, was reported to produce antinociceptive effects when administered systematically (Calderon et al., 1994). Subsequently, an additional DOR agonist, ARM390, was developed, which is structurally related to SNC80 and was able to reduce myocardial infarct size without causing convulsions (Watson et al., 2006). Tan-67, a potent and selective DOR agonist, was shown to induce antinociceptive effect when administered subcutaneously (Saitoh and Nagase, 2018). Tan-67 seems to protect the heart and brain tissue from hypoxic damage and ischemic stroke through the interaction with DOR (Tian et al., 2008; Min et al., 2018). In support of this, our recent observation showed that Tan-67 is effective agent for neuroprotection in post-ischemic stroke mice (Min et al., 2018). Kent-127 is an analog of Tan-67 and structural modification of Kent-127 led to another DOR agonist, Syk-153, with improved activity (Ida et al., 2012). Many non-peptidic DOR agonists have been developed, some of which are analogs of their existing parent agonists (Gendron et al., 2016), which will be useful tools for investigation of DOR-mediated neuroprotection.

Activation of δ-Opioid Receptor Is Neuroprotective in Ischemic Stroke

δ-Opioid receptor mediates hypoxia-preconditioning induced neuroprotection

Severe hypoxia (such as 0.5–1% O_2 for 24–48 hours) has been found to reduce DOR expression, whereas hypoxia-preconditioning (HPC), a widely accepted neuroprotective strategy, increased DOR mRNA and protein levels (Ma et al., 2005). More importantly, blocking of DOR function by DOR antagonist abolished HPC-induced neuroprotection, supporting that DOR is responsible for mediating HPC-conferred neuroprotection (Ma et al., 2005; Zhang et al., 2006).

Activation of δ-opioid receptor in ischemic stroke mouse models

In a focal cerebral ischemic mouse model, DOR level was reduced at 1 to 3 hours in the frontoparietal cortex after the middle cerebral artery occlusion (MCAO) procedure (Boutin et al., 1999). Interestingly, DOR level was increased in the striatum following a long term (30 days) of MCAO (Boutin et al., 2007), possibly as a compensation mechanism. It has been known that ischemia causes neuronal injury in brain and pre-ischemic treatment of animals with a DOR agonist, Tan-67, functions as a preconditioning effect, and provides neuroprotection in both *in vitro* and *in vivo* (Zhao et al., 2006; Tian et al., 2008, 2013). Among the *in vitro* study, treatment with Tan-67 before 24 hours following ischemia showed reduced neuronal death in rat hippocampal slice cultures, but this effect was abolished when a DOR antagonist, 7-benzylidenenaltrexone, was in presence of the culture (Zhao et al., 2006), suggesting the important role of Tan-67 in neuroprotection in the ischemic condition. Furthermore, *in vivo* study with adult male rats treated with Tan-67 at 24 hours before the permanent right MCAO (Zhao et al., 2006) shows beneficial effect of the compound. Moreover, administration of Tan-67 at 30 minutes before MCAO, into lateral ventricle (Tian et al., 2008, 2013) or 1 hour before MCAO into tail vein (Min et al., 2018) reduces ischemic infarction and improves the neurologic outcome. However, the selective DOR antagonist, naltrindole, aggravates the neuronal ischemic injury (Tian et al., 2008). Another study using a different DOR agonist, BW373U86, showed the similar neuroprotective effect in a rat stroke model but intriguingly, this neuroprotection appears to be DOR-independent (Kao et al., 2008).

Clinical studies

Despite numerous clinical studies of DOR agonists in other diseases, no clinical tests have been seen in stroke patients. Based on existing phase I and II clinical investigation, however, some DOR agonists appear promising. For instance, ADL5859 and ADL5747 are two non-peptidic agonists that do not produce convulsions but show good oral bioavailability, analgesic and antidepressive effects in animal studies (Nozaki et al., 2012). However, the primary endpoint (i.e., pain reduction) was not met in phase II evaluations and thus further studies were terminated (Spahn and Stein, 2017). Another DOR agonist, NP2 Enkephalin, has been completed its phase II clinical evaluation and the results for the peptidic agonist are pending (www.clinical trials.gov; Identifier: NCT01291901). These studies indicate a potential of DOR agonists in benefiting stroke patients.

Mechanisms Underlying δ-Opioid Receptor-Mediated Neuroprotection Following Stroke

Multiple mechanisms have been proposed to explain the neuroprotective effects following DOR activation in stroke studies. Here, only three mechanisms are summarized, which include activation of extracellular regulated protein kinase, p38 mitogen-activated protein kinase (MAPK) as well as the downstream brain-derived neurotrophic factor (BDNF)-tropomyosin receptor kinase B (TrkB) signaling pathways (Tian et al., 2013; Sheng et al., 2018), activation of the phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway (Lv et al., 2017), and altered expression and processing of amyloid precursor protein (APP) (Min et al., 2018).

Activation of extracellular regulated protein kinase and p38 MAPK signaling pathway

To achieve neuroprotection, HPC has been suggested to be an effective strategy but the underlying mechanisms have been uncertain. *In vitro* studies suggest that DOR-mediated HPC neuroprotection relied on increased extracellular regulated protein kinase and Bcl-2 activity and downregulation of p38 MAPK activities and cytochrome c release (Ma et al., 2005). In this condition, p38 is deleterious for neuronal survival. DOR activation-mediated neuroprotection appears involving the BDNF. During ischemic injury, BDNF binds to the TrkB receptor, leading to reduction of the TrkB receptor level and neuronal injury (Tian et al., 2013; Sheng et al., 2018). In contrary, the DOR activator Tan-67 reverses the ischemic effect and provides neuroprotection (Tian et al., 2013) and reduces

neuroinflammation (Sheng et al., 2018). These results support that preconditioning of Tan-67 has a major role in neuroprotection in both *in vitro* and *in vivo* models of ischemic stroke via BDNF-TrkB signaling pathway.

Activation of phosphatidylinositol 3-kinase-Akt signaling pathway

In a rat model of chronic glaucoma, treatment of the animal with SNC121, an analog of SNC80 that is a highly selective non-peptide DOR agonist, protected retina ganglion cells against glaucomatous injury and activated the PI3K/AKT signaling pathway (Husain et al., 2017). Moreover, the neuroprotection effect conferred by SNC121 was dependent on PI3K/AKT pathway. Studies in ischemic stroke models also support the role of this pathway in mediating neuroprotection of DOR agonists. Similarly, administration of DADLE (D-Ala2, D-Leu5-enkephalin), a synthetic peptide DOR agonist, reduced cerebral infarct volume as well as apoptotic cells, whereas inhibition of PI3K-Akt pathway abolished the agonist mediated beneficial effect, indicating a significant role of PI3K-Akt pathway in promoting neuroprotection of DADLE against ischemic stroke-caused brain injury (Lv et al., 2017).

Altered amyloid precursor protein expression and processing

Various studies indicate stroke as a common risk factor for dementia and Alzheimer's disease (Imfeld et al., 2013; Santos et al., 2017). It has also been known that the APP plays an important role in the pathophysiology for this neurodegenerative condition (Hefter and Draguhn, 2017). APP is a transmembrane glycoprotein, abundantly expressed in the brain and upregulated during neuronal maturation and differentiation (Ovchinnikov et al., 2018) and during traumatic brain injury (Itoh et al., 2009). Further, the expression and processing of APP are altered in ischemic stroke (Hiltunen et al., 2009; Hefter and Draguhn, 2017), while the DOR agonist, Tan-67, is able to reverse stroke-induced alteration of APP expression and processing (Min et al., 2018). Proteolytic cleavage of APP results into formation of soluble APP, which induces axonal outgrowth and attenuates neuronal death (Nhan et al., 2015), suggesting that increased expression and processing of APP plays an important role in neuroprotection (Chasseigneaux and Allinquant, 2012; Plummer et al., 2016; Dorard et al., 2018). On the other hand, the deposited plaque from amyloid beta (Aβ) peptide is thought to play a central role in Alzheimer's disease-like pathogenesis that contributes to vascular dementia and enhances neuronal death in brain following stroke (Sun et al., 2015). These data indicate that the expression and processing of APP are crucial for the neuroprotection against stroke induced neuronal consequences and for improving functional outcome during the early stage of stroke. However, the increased expression and processing of APP is likely deleterious during late or recovery stage of ischemic stroke due to the neurotoxic effect of elevated amyloid-β.

In addition to understanding of the role of Tan-67 in pre-ischemic stroke, we have also studied the effect of Tan-67 in stroke mice after MCAO (Min et al., 2018). Post-ischemic administration of Tan-67 reduces infarct volume by 20% in MCAO induced brain injury and treatment with its antagonist, naltrindole, abolishes the observed protection. Further, the MCAO procedure results in loss of neurons. However, the post-treatment of Tan-67 rescues neuronal cell death, and enhances the animal survival and functional recovery as evidenced by low neurological deficit score after ischemic stroke. Consistent with preconditioning effects of Tan-67, these post-ischemic results suggest that Tan-67 may have potential effect for neuroprotection and improved survival in post-ischemic condition. As described previously, the APP level is altered in different animal models of acute hypoxia-ischemia and traumatic brain injury (Hefter and Draguhn, 2017). We observed a similar effect in our ischemia/reperfusion stroke mouse model. There is significant reduction of APP level at early post-ischemic stage (6 hours) (Min et al., 2018). However, the post-ischemic treatment of Tan-67 increases APP expression, maturation and processing at early time point, raising the possibility that the increased level of APP may protect neurons from ischemic damage at early stage. Furthermore, our study showed MCAO also induced an increase in APP level at late stage (24 hours) (Min et al., 2018) consistent with earlier reports (Hiltunen et al., 2009). In contrast to early time point, post-ischemic treatment of Tan-67 decreases the APP levels in the penumbral cortex at a late time point, suggesting that persistent increased level of APP is not required in the brain cells, as that may produce increased level of toxic Aβ peptides to induce neuronal death. These data suggest that Tan-67 mediated neuroprotection following ischemic stroke may be through the expression/processing of APP as illustrated in detail in **Figure 1**. However, cleavage of APP by β- and γ-secretases is a key to amyloid plaque formation in AD. The expression of β-secretase, β-site APP cleaving enzyme (BACE1), increases in the brain and colocalizes with the intracellular the sites of Aβ production, suggesting an essential role of BACE1 in the generation of Aβ (He et al., 2014). Moreover, the transient cerebral ischemia causes an increase in β-secretase activity, and BACE1 colocalizes with apoptotic cells (Wen et al., 2004), leading to enhanced caspase activation and Aβ aggregation (van Groen et al., 2005; Pluta et al., 2013). Thus, it is possible that ischemic stroke acts as a trigger for sporadic AD (Pluta et al., 2013, 2018). However, Tan-67 treatment reduced β-secretase activity and suppresses BACE1 upregulation in post-ischemic condition (Min et al., 2018) that may mediate neuroprotection. Taken together, these data support the therapeutic role of DOR agonists in ischemic stroke and other diseases such as Alzheimer's disease.

Besides above described explanations, there are possible other mechanisms to elucidate DOR-mediated neuroprotection. Since ischemic stroke involves pronounced alterations in neurons at both cellular and molecular levels, including increased oxidative stress (Liu et al., 2014; Min et al., 2017), impaired proteostasis (Liu et al., 2016, 2019), and elevated neuroinflammation (Lu and Wang, 2012; Chen et al., 2016; Simats et al., 2016), it is possible that the DOR agonists may activate multiple signaling pathways (Polo et al., 2019), including nuclearfactor erythroid-2-related factor-2/heme oxygenase-1/NAD(P)H dehydrogenase quinone 1 signaling pathway, to exert neuroprotective effects in the context of stroke condition.

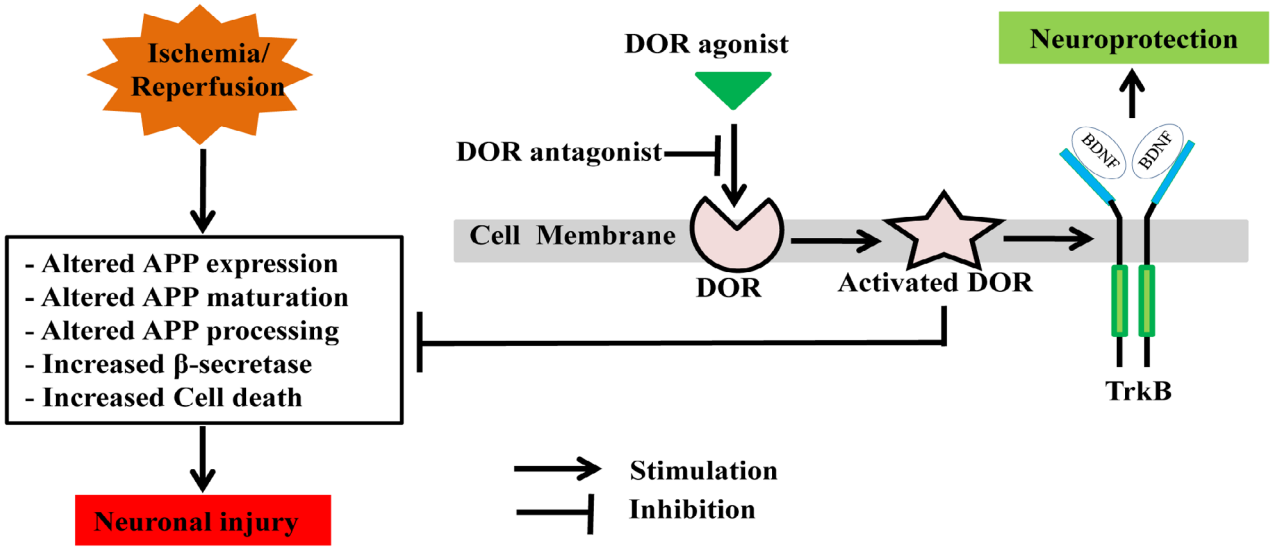

Figure 1 Schematic diagram illustrating neuroprotective effect of a δ-opioid receptor (DOR) agonist on ischemic stroke-caused brain injury. Ischemia alters the expression, maturation and processing of amyloid precursor protein (APP) and enhances β-secretase and cell death, thereby promoting cell injury. However, activation of DOR upregulates brain-derived neurotrophic factor (BDNF)-tropomyosin receptor kinase B (TrkB) signaling, reducing ischemic stroke-induced neuronal injury. Additionally, activation of DOR reverses ischemia-caused alteration of APP, thereby enhancing neuroprotection. The effects of activation of DOR are abolished in presence of a DOR antagonist (Min et al., 2018).

Conclusions and Future Perspectives

DOR has increasingly become attractive therapeutic target for treating ischemic stroke-caused neuronal injury due to activation of DOR induces potent neuroprotection. Over the last two decades, many highly selective and potent DOR agonists have been developed. The activation of DOR by these agonists and inhibition of the receptor by antagonists provide significant potential platforms for health and vitality of neuronal cells. In addition to this, the DOR signalling seems to be involved in various cellular processes and may be useful for studying the pathophysiological mechanism for ischemic stroke in the future. Above all, it looks quite evident from our and other's experimental models of ischemic stroke that those selective non-peptide DOR agonists may serve as a therapeutic agent for ischemic stroke in the future. However, a major concern for use of these agonists in treating stroke may be their side effects, which include convulsions, suppression of gastrointestinal transit, respiratory depression, abuse potential, as well as proconvulsant activity. With development of additional novel or structurally modified DOR agonist, it has become possible to minimize or to completely eliminate these adverse effects. Indeed, some severe side effects, such as convulsions, disappear in some newly developed agonists or the analogs when compared to the existing or the parent agonists. Given the fact that DOR agonists mediate different signaling pathways, combination of DOR agonists with additional specific signaling pathway modulators may cause the greatest neuroprotective efficacy with the best tolerated side effects. On the other hand, since activation of DOR alters APP expression and processing, DOR agonists may be useful in treating stroke-induced vascular dementia or Alzheimer's disease. This possibility will be significantly enhanced by developing more potent, longer-lasting, and better-tolerated agonists, as well as better understanding of DOR-mediated intracellular signaling pathways. New discoveries in the field will certainly open new avenues in treating other neurological disorders.

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