The imidazoline receptors and ligands in pain modulation

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ABSTRACT

Pain is an unpleasant experience and effects daily routine negatively. Although there are various drugs, many of them are not entirely successful in relieving pain, since pain modulation is a complex process involving numerous mediators and receptors. Therefore, it is a rational approach to identify the factors involved in the complex process and develop new agents that act on these pain producing mechanisms. In this respect, the involvement of the imidazoline receptors in pain modulation has drawn attention in recent years. In this review, it is aimed to focus on the imidazoline receptors and their ligands which contribute to the pain modulation. It is demonstrated that imidazoline-2 (I_2) receptors are steady new drug targets for analgesics. Even if the mechanism of I_2 receptor is not well known in the modulation of pain, it is known that it plays a role in tonic and chronic pain but not in acute phasic pain. Moreover, the I_2 receptor ligands increase the analgesic effects of opioids in both acute and chronic pain and prevent the development of opioid tolerance. So, they are valuable for the chronic pain treatment and also therapeutic coadjuvants in the management of chronic pain with opiate drugs due to the attenuation of opioid tolerance and addiction. Thus, the use of the ligands which bind to the imidazoline receptors is an effective strategy for relieving pain. This educational forum exhibits the role of imidazoline receptors and ligands in pain process by utilizing experimental studies.

KEY WORDS: Acute pain, chronic pain, imidazoline receptors, imidazoline receptor ligands

Introduction

Pain is defined as an unpleasant sensory and emotional experience arising from any part of the body. It is associated with actual or potential tissue damage or described in terms of such damage by International Association for the Study of Pain. It is an "experience" and in this respect, it differs from "nociception." Nociception is called a neural process that provides transduction and transmission of a noxious stimulus to the brain via pain pathways. The pain arises from a complicated interaction between signaling systems, modulation of higher centers, and individual perception.[1,2]

The whole human population experiences pain in varying degrees and daily routine is affected negatively. Pain may be occurred acutely or chronically related with various disturbances such as lesions, traumatic injury, tumors, inflammatory diseases, Parkinson's disease, and diabetes.[3,4] Since different mechanisms involve in the pathophysiology of acute and chronic pain and even nociceptive and neuropathic pain, the management strategies and current drug classes also vary. Although there are too many analgesic agents, there are certain problems such as tolerability, tolerance, abstinence syndrome, insufficiency, possible drug interactions, and side effects. Thereby, the development of new analgesic compounds is still going on. In this respect, the development and the use of imidazoline receptor ligands have gradually drawn attention since the role of imidazoline receptors in pain modulation was identified. For instance, various ligands which bind to imidazoline-2 (I_2) receptors, the imidazoline receptor

subtype which is predominantly involved in pain modulation, have been synthesized 2-(4,5-dihydroimidazole-2-il) quinoline hydrochloride (BU224), 2-(2-benzofuranyl)-2-imidazoline hydrochloride (2-BFI), 4-chloro-2-(imidazoline-2-yl) isoindoline (RS-45041), etc., in last decades and all of them have been reported to exhibit antinociceptive properties as discussed in this review.[5-7] Whereas the single use of imidazoline receptor ligands is effective in tonic and chronic pain, combined usage of other analgesic drugs such as morphine and clonidine is also effective in the potentiation of both acute and chronic pain conditions such as neuropathic pain. In fact, it is known that the I_2 receptor agonism is one the mechanisms of neuropathic pain control, and the ligands that use this mechanism are in the phase 2 and phase 3 studies.[8-10] In this review, we document the role of I_2 receptors and ligands in antinociception and the relevant experimental studies performed by various researchers.

Imidazoline Receptors and Their Biologic Roles

Although the term imidazoline receptor has not yet been adopted by major professional societies including "International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification" since these receptors have not yet been cloned and the signaling pathway not characterized, this term is widely used in the literature.[11] Therefore, it is also frequently called as imidazoline binding sites; however, the term imidazoline receptor is employed in this review.

The presence of imidazoline receptors, with high affinity for imidazoline subdivision containing compounds, first became apparent in the mid-1970. The hypotensive effect induced by clonidine, α_2-adrenoceptor agonist, and microinjection into the rat brainstem was not mimicked by norepinephrine.[12] The imidazoline receptors are broadly located in the mammalian cells of the central nervous system (CNS) and peripheral nervous system[13] and contribute to cardiovascular system activity, gastric acid secretion, insulin release, antinociception, Alzheimer's, and Parkinson's disorders.[14] According to a general opinion, there are three main classes of heterogeneous imidazoline receptors, as seen in Figure 1. Imidazoline-1 (I_1) receptors constitute a family of nonadrenergic high-affinity binding sites for some ligands such as clonidine and idazoxan. These receptors handle the centrally mediated hypotension occurred with clonidine-like drugs.[15] They are located in the plasma membranes in the brain, heart, kidney, liver, and pancreas. The I_2 receptors bind imidazolines and guanidines and have a lower affinity for 2-aminoimidazolines such as

**Figure 1:** The imidazoline receptors in pain

clonidine.[16] The I_2 receptors are mitochondrial, not G-protein coupled, and allosteric binding sites, possibly with a modulatory function, on monoamine oxidase-A and -B (MAO-A and -B). These enzymes are found in the neurons and astroglia cells and have a critical role in the inactivation of neurotransmitters. Thereby, the I_2 receptors may be useful as a therapeutic agent in various neurological diseases in which neurodegeneration is observed.[14,15] Besides, it is known that these subtypes contribute to reduce body temperature, exert control over central noradrenergic and hypothalamic-pituitary-adrenal axis activity, and regulate the small intestinal motility.[17,18] More remarkably, it has been shown that the I_2 receptors take part in the antinociception in several acute and chronic pain models and the ligands acting on the I_2 receptors may be assessed as novel analgesics.[19] The imidazoline-3 (I_3) receptors whose biological importance investigated further, are present in the pancreatic beta islet cells and modulate insulin secretion.[16] We focus on the I_2 receptor subtypes in this educational forum because involvement of this subtype in antinociception is well determined.

Imidazoline-2 Receptors in Pain Modulation

Pain modulation is a highly complex process, including numerous interacting peripheral and central mechanisms. The activation of the peripheral nociceptors or mediators that are released by the damaged tissue is required for the perception of pain. The activation-triggered signal is conveyed with the afferent transmission to the spinal cord with Aδ and C nerve fibers and transmission parts through the dorsal horn (DH) to the higher centers via parallel ascending pain pathways.[20] The impulses originated from the brain stem nuclei, descend to the spinal level and affect the transmission of pain signals at the DH.[9,21] The relative balance between descending inhibition and facilitation can be changed by the type and intensity of the stimulus and also by the time following an injury.[8] This complex process is regulated by the interaction of various chemicals and receptors over an extensive network from the periphery to the CNS. The rate of participation of the chemicals and receptor types in the modulation depends on the types of pain and noxious stimulus.

The imidazoline receptors that are taken part in this extensive receptor networks have gradually gained important in the recent years. When the roles of imidazoline receptors are evaluated in terms of pain, I_2 subtypes attract the attention.[22] the I_2 receptors are distributed ubiquitously throughout the brain regions such as the arcuate nucleus, caudate nucleus, putamen, globus pallidus, substantia nigra, interpeduncular nucleus, area postrema, mammillary peduncle, ependyma, lateral mammillary nucleus, and the pineal gland. Low to moderate densities are found in the cerebral cortex, thalamus, hippocampus, amygdala, inferior olivary nucleus, ependymal, and various periphery regions.[16] The I_2 receptors are characterized by their high affinity for imidazolines and guanidines and medium affinity for imidazolidines. Also, they have two subtypes as I_{2A} and I_{2B}, which differ in terms of their sensitivity to amiloride.[23] The I_2 receptor is first located on the outer membranes of mitochondria and as allosteric sites on enzyme MAO-A and MAO-B.[24] However, the imidazoline binding
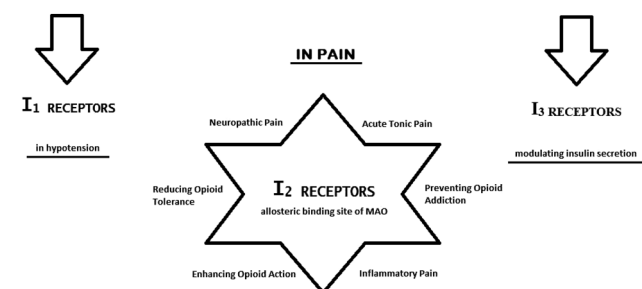
site on MAO is separate from the active domain of the enzyme that recognizes the mechanism-based inhibitors, and it is not equally available in all the tissues.[25] The I_2 receptors have the same molecular weight as MAO, and the amino acid sequencing of purified I_2 receptors is similar to MAO.[26]

Two MAO isoforms play a fundamental role in the metabolism of monoamine neurotransmitters such as serotonin, noradrenaline, and dopamine.[27] As the I_2 receptor is thought to be a modulatory site on the MAO protein, the activity of I_2 receptors may involve in several neurological disorders.[24,27] Another fascinating development with I_2 receptors is that its effect on nociception since these monoamines appear to play a significant role in specific CNS structures implicated in pain modulation spinal cord, cerebral cortex, etc., and are involved in the antinociception of several drugs such as antidepressants which are commonly used for the management of pain.[27] The ligands binding to the I_2 receptors can be considered as inhibitors of MAO-A and MAO-B since they inhibited monoamine oxidation,[28] and this inhibition could explain some biological effects of imidazoline receptor ligands such as pain modulation.[29] In fact, it is well identified that increased levels of monoamines such as serotonin and noradrenaline contributes to pain control, especially in the CNS regions related to pain. The drugs such as MAO inhibitors, serotonin noradrenaline reuptake inhibitors, and selective serotonin reuptake inhibitors that provide the enhancement of levels of these neurotransmitters are successfully being used to relieve various pain conditions.[30-32]

Some evidence that shows the I_2 receptors contribute to the modulation of pain [Figure 1] reports that the ligands that affect I_2 receptors are effective for tonic pain, neuropathic pain, but little effective for acute pain.[11] Moreover, the activation of I_2 receptors has been suggested to be a way of enhancing opioid analgesic actions.[10] When they are combined with opioids, the I_2 receptor ligands increase the analgesic effects of opioids in both acute and chronic pain. In chronic use, tolerance and addiction to the opioids can develop. However, the I_2 receptor ligands can reduce the development of this opioid tolerance or prevent from deprivation syndrome that is triggered by the antagonists in animals.[11] When all of these findings are considered together, ligands that affect the I_2 receptors can be beneficial in monotherapy or combination therapy with opioids to overcome pain. Therefore, various new selective ligands are being developed for this receptor types.

Imidazoline-2 Receptor Ligands in Pain

Although the I_2 receptors and their signaling pathways have not yet been characterized, the majority of the I_2 receptors are widely accepted as being allosteric sites on MAO. Therefore, the I_2 receptor ligands are described as allosteric modulators. Allosteric modulation is the modulation of a protein via binding a ligand to the domain that is distinct from the active site of the protein. Conformational change occurs by this binding process. Ligands that improves the activity of the protein are referred as allosteric activators or agonists, whereas those that decrease the activity of the protein are referred as allosteric inhibitors or antagonists.[33] In principle, it is not precisely known whether a ligand is an I_2 receptor agonist, an antagonist, or an inverse agonist in a constitutively active system. Each and every ligand has two properties (i.e., affinity and efficacy) that govern its effects related to certain receptors in a bioassay.[34] It is possible to have a knowledge of the relative efficacy of these ligands by systematic comparison. Ligand efficacy values may vary depending upon assays, however, the rank order of their efficacy remains unchanged with few exceptions (e.g., functional selectivity).[11]

Idazoxan, agmatine, and clonidine are ligands that bind to the I_2 receptors as well as α_2 and/or I_1 receptors with varying affinities. Due to the proven effect of the I_2 receptors in pain, further studies are required to discover selective analgesic I_2 receptor ligands and to elucidate their physiological functions. Over the last few decades, investigators have attempted to synthesize and recognize selective ligands for the I_2 binding sites. For instance, the I_2 receptor ligand 2-BFI (pK$_i$ = 8.47 for I_2 in rabbit kidney membrane with [^{3}H] 2-BFI) which has high affinity for both I_{2A} and I_{2B} sites has been used to characterize these sites in several species, including humans.[26] It is also extremely useful for binding and autoradiographic studies.[35] BU series have also been investigated in the previous years. It has been proved that quinolone compound BU224 has high affinity (pK$_i$ = 8.43 for I_2 in rabbit kidney membrane with [^{3}H] 2-BFI)[26] for the I_2 receptors over I_1 receptors and α_2-adrenoceptors, among all the compounds of BU series.[26,35] RS-45041-190 is also a selective ligand with a high affinity (pK$_i$ = 9.37 for I_2 in rabbit kidney membrane with [^{3}H] idazoxan)[36] for the I_2 site which exhibits comparable data to that observed using 2-BFI in membrane-binding and autoradiographic studies.[26]

As mentioned before, the imidazoline receptor ligands are declared to modulate certain processes which involve MAO activities in CNS.[29] The studies reveal that among all of the imidazoline receptor ligands those mentioned in this review; 2-BFI, BU224, 2-phenyl-6-(1H-imidazol-1il) quinazoline (CR4056), idazoxan, and RS-45041 more selectively inhibit MAO-A while LSL60101 and LSL61122 inhibit MAO-B.[13,36-38] After this part of the review, several studies will be conducted with the mentioned ligands [Figure 2] that have a higher affinity for the I_2 receptors and the provided results will be included.

It should first be noted that clonidine that mediated the discovery of the presence of imidazoline receptors, is a α_2-adrenoceptor agonist that binds not only to $\alpha_2$adrenoceptors but also to imidazoline receptors in particular to I_1 receptors compared to I_2 receptors; however, its antinociceptive activity occurs via α_2-adrenoceptors rather than imidazoline receptors.[39] Agmatine is a nonselective and most extensively

Figure 2: The imidazoline imidazoline-2 receptor ligands in pain
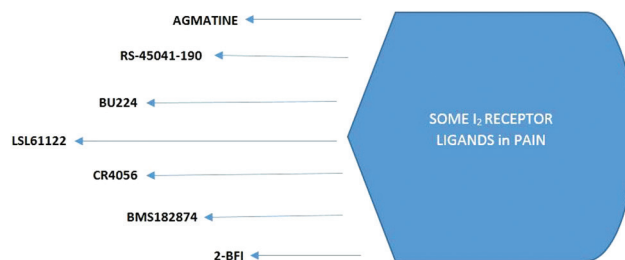
studied endogenous imidazoline receptor agonist, and has a moderate affinity to α_2-adrenoceptors as well as all subtypes of imidazoline receptors ($pK_i < 5$ for I_2 in rabbit kidney membrane with [^{3}H] 2-BFI).[26,40] Its effect on spinal nociception is known. It is indicated that this endogenous substance prevents reflex respond to the noxious stimulus through nonadrenergic receptors in mice.[29] It does not show a significant effect on acute phasic pain while it is vice versa in the acute tonic (differs from acute phasic pain in terms of using chemicals to induce noxious stimuli), inflammatory, and neuropathic pain. The effectiveness of agmatine also depends on the administration route in acute pain. Although agmatine showed weak effectiveness in a few studies,[41] in many others, it was not efficient when administered systemically in acute phasic pain.[42] Spinal and supraspinal agmatine administration also does not reduce the thermal threshold, similar to systemic agmatine treatment. For example, in a study, i.t. (spinal) and also i.c.v. (supraspinal) agmatine administration did not produce analgesic effects in the tail-flick test in mice.[43] Conversely, agmatine is effective in inflammatory pain. The acute systemic agmatine treatment markedly decreased mechanical allodynia induced by complete Freund's adjuvant (CFA), chronic pain model, in mice.[44] Agmatine injections by systemic and supraspinal route have also been demonstrated to be effective in relieving hyperalgesia and/or allodynia in several neuropathic pain models.[22]

Some other similar substances have also showed the same results. Systemic administration of the I_2 receptor ligands as phenyzoline, 2-BFI, 2-(2-benzofuranyl) imidazole hydrochloride (LSL 60101); the analog of 2-BFI, 2-styryl-2-imidazoline; valldemossine or tracizoline (LSL 61122) also did not produce antinociception in the acute pain model.[29,45] In addition, researches showed that the I_2 receptor ligands such as RS-45041-190, CR4056, 2-BFI, BU224 were effective in inflammatory and neuropathic pain.[6,7,46]

RS-45041-190, the first selective and high-affinity ligand, showed significant results on the carrageenan-induced thermal and mechanic hyperalgesia tests when administered systemically (i.p.), not spinally (i.t.) in rats.[7] CR4056 (moderate affinity I_2 receptor ligand (IC_{50} = 596 nM, in rat whole brain membrane with [^{3}H] 2-BFI),[13] is a new, highly selective I_2 receptor ligand which inhibits MAO-A activity more selectively than MAO-B. In a study, the effectiveness of CR4056 was evaluated in various models of pain. CR4056 was found active in CFA-induced model of inflammation. In acute capsaicin-evoked pain model, CR4056 blocked the paw-induced mechanic hyperalgesia.[13] This effect was antagonized by idazoxan (pKi = 7.22 for I_2 in rabbit kidney membrane with [^{3}H] 2-BFI),[26] which is both a α_2-adrenoceptor and I_2 receptor antagonist. CR4056 also significantly reduced the mechanic hyperalgesia and allodynia in neuropathic pain models.[13] Similarly, in another study, CR4056 oral administration dose-dependently reversed the allodynia in bortezomib-induced peripheral neuropathy model that is painful.[46] The postoperative pain is apparently distinct from pure inflammatory or neuropathic pain. More recently, Lanza *et al*.,[47] have investigated the antinociception induced by CR4056 in a rat model of postoperative pain and Caselli *et al*.,[48] in a rat model of joint pain. Acute administration of CR4056 was found effective in relieving postoperative pain and joint pain as well as

inflammatory and neuropathic pain. Even naproxen showed low and nonremarkable antinociception compared to antinociception induced by CR4056 in these pain models. In addition, in joint pain model driven by both nociceptive and neuropathic mechanisms, the rats treated for 7 days (from days 14 to 21) after the induction of cartilage degeneration with CR4056, showed a significant reduction of both basal pain behaviors (allodynia and hyperalgesia). This result demonstrates either a long lasting effect or even an actual symptom modifying effect. The joint pain model is related to osteoarthritis that is driven by both nociceptive and neuropathic mechanisms.[48] Shortly, these studies present a new opportunity for the management of inflammatory, neuropathic, postoperative, and joint pain based on the selective interactions with the central I_2 receptors. The phase II trials on neuropathic pain for CR4056 are available and still going on. The effect of BU224, a high affinity selective I_2 receptor ligand, has been assessed electrophysiologically on the nociceptive neurons' responses in the spinal DH. Spinal injection of BU-224 by i.t. route attenuated the nociceptive responses of DH neurons, creating a dose-dependent inhibition of C-fiber-induced responses, Aδ-fibre-evoked responses, post discharge, and winding-up of the cells. Idazoxan (i.t.) completely and significantly antagonized these effects while the nonselective α_2-adrenoceptor antagonist yohimbine and the highly selective α_2-adrenoceptor antagonist atipamezole only partially antagonized.[5] When we consider the results, it is possible to say that BU224 has a high affinity for the spinal I_2 receptors, as well as it has an insignificant action at the spinal α_2-adrenoceptor receptors. It is obvious that the I_2 receptor ligands are more effective in chronic pain models than acute phasic pain models as mentioned with agmatine. Chronic pain usually means a persistent pain lasting 3 months or more, and pharmacotherapy of chronic pain always comprises repeated dose. A possible result of repeated doses of analgesics is a gradual decrease in analgesic effect, in other words, development of analgesic tolerance. From this point of view, in a research performed by Li *et al*.,[6] antihyperalgesic effects of 2-BFI and CR4056 have also been tested in repeating treatments, in addition to single doses in chronic constriction injury (CCI)-induced neuropathic pain and CFA-induced inflammatory pain models. The antinociceptive tolerance did not develop against repeated administration (daily for 7–9 days) of 2-BFI or CR4056 in CFA-treated or CCI rats. It is possible to say that the repeated dose regimen for the I_2 receptor ligands in chronic pain treatment may be useful as monotherapy or adjunctive therapy without tolerance and addiction. It has been also shown that three high selective I_2 receptor ligands; 2-BFI, BU224, and LSL 61122 possess antihyperalgesic effects in the rat models of CFA evoked inflammatory pain in this study. These drugs reduced mechanical and thermal hyperalgesia in a dose-dependent manner. Also, the I_2 receptor antagonist idazoxan antagonized the antihyperalgesic effects of 2-BFI in CFA-treated and CCI rats.[6] These data also support the beneficial roles of the I_2 receptor ligands in pain control. Pain models contain lots of irrelevant and interacting compounds. Although most parts of preclinical pain studies focus on sensorial relieving pain, the sensorial and emotional compounds should be studied together. For instance, the effects of the I_2 receptor ligands such as 2-BFI, BU224, and CR4056 on escape/avoidance behaviors on CFA injected rats were studied connectedly to the affective pain in the

same study. This method is suitable to measure the dissociable components of effective pain which is different from the sensory pain. It was observed that 2-BFI, BU224, and CR4056 increase the escape/avoidance behavior in the hyperalgesia increasing doses.[6] These results exhibit that the I$_2$ receptor ligands may be effective against the affective components of pain. More recently, Thorn *et al*.[49] have studied the antinociception induced by 2-BFI and phenyzoline, high affinity ligand for I$_2$ receptors (pKi = 8.60 in rabbit kidney membrane with [^{3}H]-idazoxan),[45] using the von Frey filament test in rats with CFA-induced inflammatory pain. Providing antinociception by 2-BFI was not surprising, however, phenyzoline also produces antinociception in this chronic model as in acute phasic pain under weak noxious stimulus, as reported previously in a study by Sampson *et al*.[50]

The role of imidazoline receptors for enhancing morphine antinociception is also known. Even some I$_2$ receptor ligands as agmatine are not effective alone in acute phasic pain, they potentiate morphine antinociception.[42] In a study, performed in the warm water, tail withdrawal procedure in rats by using selective I$_2$ receptor ligand 2-BFI along with agmatine, it was observed that these two ligands increase the antinociceptive effects of morphine and tramadol. In contrast, another selective I$_2$ receptor ligand BU224 failed to increase the antinociceptive efficacy but prevented agmatine and 2-BFI ligands to increase the morphine and tramadol-induced antinociception. The reason that BU224 acts differently from other imidazoline receptor ligands is its lower efficacy in spite of its high affinity.[51] This contradictory situation may be confusing, but it should be noted that affinity and efficacy are distinct terms from each other. A ligand that shows low efficacy may bind its binding site with high affinity.[52] In yet another study, the combination of 2-BFI and morphine produced additive effects on mechanical hyperalgesia in CFA-treated rats.[6] These results suggest that the combination of the I$_2$ receptor ligands and opioids may be effective in chronic pain treatment. However, the previous studies indicated the I$_2$ receptors to contribute potentiation mechanism, and I$_1$ and I$_2$ receptors' contribution of potentiation mechanism was not clearly understood. More recently, a study which has been done to understand which subtype contributes to potentiation mechanism showed that a significant oxycodone-induced antinociceptive respond could not be reversed by efaroxan (I$_1$ receptor antagonist) but could be reversed by BU224 (I$_2$ receptor antagonist). As a similar way, endothelin ET$_A$ receptor antagonist 5-(Dimethylamino) -N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide-induced potentiation of oxycodone antinociception was reversed by BU224 but not efaroxan.[53] So, it is thought that the I$_2$ receptors participate in the potentiation, the I$_1$ receptors do not. In yet another study performed for understanding the importance and mechanisms of potentiation, agmatine, high selective and more powerful substances such as 2-BFI, LSL 60101 (pK$_i$ = 6.45 for I$_2$ in rat cerebral cortex with [^{3}H] idazoxan),[54] LSL 61122 (pK$_i$ = 8.74 for I$_2$ in rabbit kidney with [^{3}H] idazoxan),[55] and aganodine have been tested. It was observed that central (i.c.v.) or peripheral (s.c.) administration of the I$_2$ receptor ligands (but not I$_1$ or α$_2$adrenoreceptor) potentiate the morphine-evoked supraspinal antinociception in mice. The enhanced morphine antinociception via the I$_2$ receptor ligands was reversed by idazoxan, BU224, and isothiocyanatobenzylimidazoline, an irreversible I$_2$ antagonist. In the same study, it has also been shown how the augmentation of morphine antinociception by the I$_2$ agonists' changes in mice with pertussis toxin impaired guanosine triphosphate-binding G$_i$-G$_o$ proteins. The potentiation ability effect was blocked. Therefore, the contribution of G$_i$-G$_o$ transducer proteins in the modulation of morphine antinociception induced by the I$_2$ receptors cannot be disrespected.[29] Most recently, Thorn *et al*.[49] studied 2-BFI and phenyzoline with oxycodone as combinations, separately. 2-BFI and oxycodone produced additive interactions while phenyzoline and oxycodone produced synergistic interactions for their effects on mechanical hyperalgesia in CFA-treated rats.

The imidazoline receptors are also important for the tolerance developed with opioids as well as improvement of opioid analgesia as mentioned before. For instance, agmatine prevents or decreases the tolerance development against morphine or other opioids.[56] Additionally, α-difluoromethylornithine and aminoguanidine, which may affect the metabolism of endogenous agmatine, were found effective in the inhibition of acute morphine tolerance in tail-flick test.[57] Similarly, Boronat *et al*.,[58] have assessed the role of imidazoline receptors in opioid (morphine and pentazocine) tolerance in rats by the administration of idazoxan. The tail-flick test was used for evaluating the antinociception. Idazoxan completely prevented the morphine tolerance, but 2-methoxy-idazoxane and RS-15385-197, selective α$_2$-adrenoceptor antagonists, did not and it remarkably reduced tolerance to pentazocine.[58] In contrary, Su *et al*.,[59] showed that idazoxan promoted the development of tolerance to morphine and induced the abstinence syndrome in morphine-dependent mice and rats similar to naloxone. The chronic concurrent administration of 2-BFI, LSL 60101, and LSL 61122, selective and potent I$_2$ receptor ligands, and morphine, also prevented or attenuated morphine tolerance.[58] In the light of the positive outcomes, it is supported that the I$_2$ receptor ligands as promising therapeutic coadjuvants in the management of chronic pain with opiate drugs since these agents prevent tolerance development and enhance opioid analgesia.

Conclusion

All the studies show us that the I$_2$ receptors are also steady, new drug targets for analgesics. Even if the mechanism of the I$_2$ receptor is not well known in the modulation of pain, it is known that it plays a role in tonic and chronic pain but not in the acute phasic pain. Additionally, when they are combined with opioids in both acute and chronic pain, the I$_2$ receptor ligands increase the antinociceptive actions of opioids. The development of tolerance and addiction induced by chronic administration of opioids is one of the major problems in the clinic. However, the I$_2$ receptor ligands can reduce the opioid tolerance development or prevent from deprivation syndrome in the combination therapy. They are valuable for the chronic pain treatment and also valuable as therapeutic coadjuvants of opiates, because of the attenuation of opioid tolerance and addiction.

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