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Implications of the imidazoline system in the human brain

Mihai **Nechifor**[1]*

[1] Department of Pharmacology, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania

*** Correspondence to:** Mihai Nechifor, Department of Pharmacology, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania. Phone: +40744508642; E-mail: mihainechif@yahoo.com

Abstract

The imidazoline system is formed by the imidazoline receptors I1, I2 and I3 and the natural competitive agonists that have been identified in the human and animal body: agmatine, harman, harmalan and imidazole-4-acetic acid-ribotide. I1 and I3 receptors are located in the cell membrane. I2 receptors are found as sites on monoamine oxidase A and monoamine oxidase B (MAO-A and MAO-B) and on the mitochondrial membrane. The brain and the cardiovascular system are the structures in the body where most actions of the imidazoline system are known. Imidazoline receptors and their natural agonists are involved in physiological processes but also in the pathogenesis of severe psychiatric and neurological disorders. The most important known implications of this system in neuropsychiatric pathology are major depression, addiction and tolerance, neurodegenerative diseases (and primarily in dementia), stress, pain and analgesia, seizures, and others. The imidazoline system is involved in normal memory and neuroprotection. This system is also important for some central nervous system vegetative functions. Stimulation of central I1 receptors causes a decrease in blood pressure, increases diuresis and natriuresis, and decreases intraocular pressure. A normal concentration of the main known agonist of imidazoline receptors, agmatine, is important for normal brain function. The plasma concentration of agmatine should be determined in all patients with mood disorders, dementia and other neurodegenerative diseases and addictions. Since only a part of agmatine is synthesized in the body and another part is provided by food intake, it is important to use foods rich in this biologically active amine. Today, only moxonidine, rilmenidine (I1 agonists) and clonidine (I1 and alpha2 agonists) are used in clinical practice in the therapy of arterial hypertension, but existing data show that there are possibilities for expanding the clinical use of imidazoline receptor agonists in the future.

Keywords: imidazoline receptors, brain, addiction, neuroprotection, mood disorders, dementias

Introduction

The imidazoline system is an endogenously active substance with receptors throughout the human body. The system consists of the Imidazoline receptors I1, I2 and I3 and their natural agonists found in the human body. The following endogenous agonists are known: agmatine, harman, harmalan, and imidazole-4-acetic acid-ribotide (IAA-RP). According to some authors, a metabolite of IAA-RP, namely imidazole-4 acetic acid riboside, can be considered an endogenous agonist of imidazoline receptors. Imidazole-4 acetic acid riboside is also an agonist of GABA receptors [1, 2]. According to current knowledge, the most studied and most important is agmatine. Agmatine is a polyamine that is synthesized from arginine by arginine decarboxylase and is metabolized under the action of agmatinase [3]. This substance is also the most widespread agonist in the human body, being identified in most organs and systems in the body. Harman is a beta carboline. Like other beta carbolines, it is an inverse agonist of benzodiazepine receptors. I1 and I3 receptors are located at the level of the cell membrane. I2 receptors have been identified at the level of MAO-A and MAO-B

(as sites located outside the active center of these enzymes) [4]. I2 receptors are also located on the mitochondrial membrane [5]. Depending on their affinity for amiloride, I2 receptors have been classified into two groups: I2 A receptors and I2 B receptors [6].

Natural selective antagonists of imidazoline receptors have not been identified in the human body to date. However, a number of antagonists of I1 and I2 receptors with greater or lesser selectivity have been synthesized. Among these antagonists, the following could be mentioned:

- I1 antagonists: efaroxan, LNP911, LNP906 and others;
- I2 antagonists: idazoxan, 2-BRI, BL-224, tracizoline, RS45041-190, LSL60101and others.

These antagonists have been and are widely used in experimental studies conducted on animals but have no clinical use.

The imidazoline system has actions and is important throughout the body, but most current data refer to its implications for the functioning of the central nervous system and the cardiovascular system.

Implications of the imidazoline system in some somatic brain functions

Imidazoline receptors I1 and I2 have been identified in many regions of the human brain and i other mammals' brainsI3 receptors are also thought to exist in the brain, but not all authors agree on this. Regarding the role of agmatine in the brain, this biogenic amine is considered a neuromodulator with important implications in the modulation of cerebral synaptic neurotransmission, transport, uptake and metabolism of some neurotransmitters [7].

The imidazoline system is involved in the normal functioning of the human brain. Disturbances in this system's functioning have been found in many pathological conditions. Disorders in the activity of the imidazoline system are thought to be involved in the pathogenesis of a number of psychiatric and neurological disorders [8, 9].

A. Pathological states

Regarding the activity of the central nervous system, the implications of the imidazoline system in the following pathological states are known: pain and analgesia; major depression; anxiety; addiction, tolerance and withdrawal syndrome; memory; cognitive decline and some neurodegenerative brain diseases; stress.

Pain and analgesia

The analgesic and antinociceptive effect of some substances, such as ethanol and nicotine, is mediated by the action of two endogenous ligands of the imidazoline receptors, namely agmatine (25 microg/icv in rats) and harmane. This effect is mediated both by the stimulation of I1 receptors and by the stimulation of I2 receptors. It is blocked by idazoxan and also by efaroxan [10]. Because idazoxan is a competitive but not very selective antagonist of imidazoline receptors (it also blocks alpha2 receptors), it is not clear how much of the analgesic-enhancing effect of ethanol or nicotine is due to its action on I2 receptors and how much is produced by blocking alpha2.Because idazoxan is a competitive antagonist of imidazoline receptors but not very selective (it also blocks alpha2 receptors), it is not clear how much of the analgesia-enhancing effect of ethanol or nicotine is due to the action on I2 receptors and how much is produced by blocking alpha2 receptors.

On the other hand, clonidine, an agonist for alpha2 and I1 receptors, potentiates the analgesic effect of tramadol. This experimental observation would support the idea that imidazoline receptors are the main receptors that increase the analgesic effect of the three substances mentioned above. However, there are important differences between the mechanisms of production of analgesia by ethanol, nicotine and tramadol, so the mechanism of this potentiation of analgesia requires further studies. Some synthetic agonists of I2 receptors (such as 2-BFI) have analgesic effectsin bothn experimental inflammatory and neuropathic pain. This analgesic effect was also abolished by idazoxan. There is an additive effect between the analgesic effect of morphine and that of 2-BFI [11]. There are some authors who believe that in the future, analgesic drugs could be produced based on imidazoline receptor agonists, but for now, such drugs do not exist [12]. Intrathecal administration of clonidine (a widely used antihypertensive drug that is an agonist on presynaptic alpha2 receptors as well as on I1 receptors) has an antinociceptive effect [13]. Agmatine potentiated the antinociceptive effect of oxycodone. Administered alone, agmatine has a more intense analgesic effect in chronic neuropathic pain but is weaker in acute inflammatory pain.

Major depression and bipolar disorders

Major depression is a severe recurrent psychiatric illness with a continuously increasing incidence and prevalence in most countries of the world. Dysfunctions of several brain neurotransmitter and neuromodulator systems, including some of the imidazoline system, are implicated in the pathogenesis of this illness. In the cerebral cortex of deceased patients with major depression, the density of I1 receptors is about 30% higher than in healthy individuals of the same age [14]. The density of cortical I2 receptors is also statistically significantly increased in these patients. Antidepressant drugs from different groups and

with different chemical structures (citalopram, fluoxetine, buspirone) reduce the density of these receptors [9, 15]. Agmatine also has an antidepressant effect experimentally demonstrated in animals [16]. TBoth types of receptors probably mediate the antidepressant effectbecause both idazoxan and efaroxan significantly reduce or suppress it. Agmatine and moxonidine reduce experimental depression in mice. Their agonist action on I1 receptors certainly mediates this effect because moxonidine is a selective agonist of these receptors [17]. Inhibition of agmatinase and increasing the concentration of agmatine in the brain also had an antidepressant effect in experimental studies. Of course, experimental data obtained with animal models of human psychiatric disorders must be translated with caution into clinical practice because no experimental model can accurately reproduce human psychiatric illness. The existing experimental results support the hypothesis that some I1 receptor agonists could, in the future, be used in the therapy of major depression, most likely in combination with other antidepressant drugs. In experimental studies in rodents, agmatine 5 mg/kg I.P. and moxonidine 0.25 mg/kg I.P. significantly potentiated the antidepressant effect of serotonin reuptake inhibitors such as paroxetine and fluoxetine. Some authors even believe that part of the antidepressant effect of the two serotonin reuptake inhibitor drugs is due to the stimulation of the activity of the imidazoline system in some brain areas [18].

Data regarding the involvement of the imidazoline system in bipolar psychosis are very few. Lithium salts did not modify the density of imidazoline receptors in these patients, but data regarding the effect of newer drugs used in the therapy of this disease are completely lacking. There is also no data regarding postmortem determinations of the cerebral density of these receptors in bipolar psychosis patients [19]. Agmatinase, the enzyme that inactivates agmatine, is strongly upregulated in hippocampal interneurons of patients with major depression or bipolar disorders [20]. This fact strongly supports the idea that an increase above normal inactivation of agmatine and a decrease in its concentration in some cerebral areas is involved in the pathogenesis of mood disorders.

Addiction and tolerance

The imidazoline system is involved in addiction and tolerance to various potentially addictive substances. In the frontal cortex of cocaine or heroin addicts, a number of imidazoline receptors were found postmortem, 60–70% higher than in normal subjects of the same age. There were no statistically significant differences between the two groups of addicted people.

The conditioned place preference (CPP) method tests the psychological dependence of animals on morphine Agmatine (0.75–20 mg/kg, s.c.) administered concomitantly with morphine in CPP induction experiments, abolishing the stimulatory effect of morphine. Agmatine reduces both physical and psychological dependence on morphine. It also reduces the intensity of the experimental abstinence syndrome in animals that received morphine. Some authors consider the cerebral imidazoline system to be a modulatory system of the action of endogenous opioids in the brain [21]. Regarding morphine addiction, an important fact is that the administration of agonists of the I2 receptors, such as 2-BFI, reduces the self-administration of morphine and also drug discrimination [22]. An incompletely explained action is the effect of agmatine to reduce the inhibitory action of zinc on the CPP-stimulating effect of morphine [23].

Nitric oxide is also involved in the production of addiction to morphine and probably to other addictive substances. There are I2 receptors on astrocytes. Stimulating these receptors by agmatine (possibly also by Harman) increases nitric oxide synthesis and (nitric oxide synthase 2) NOS2 activity. Preincubation with idazoxan (1–100 microns) of astrocyte cells significantly decreases the amount of protein corresponding to NOS2 and the amount of nitric oxide [24].

Not only is opiate and cocaine addiction influenced by the imidazoline system. Administration of agmatine(20–40 mg/kg I.P.) in rats significantly reduced ethanol self-administration in the two-bottle choice experimental test [25]. The administration of selective I1 receptor agonists such as moxonidine had the same effect, and when administered together with agmatine, it amplified its effect. The administration of selective I1 receptor agonists such as moxonidine had the same effect, and when administered together with agmatine, it amplified its effect [26]. These experimental data open the perspective of reducing ethanol dependence and chronic alcoholism by administering I1 receptor agonist drugs (rilmenidine, moxonidine and possibly others in the future).

Phencyclidine is a powerful dysleptic drug that is addictive and produces hallucinations. Both this hallucinogen and dizocilpine have as their main known mechanism of action the binding to NMDA receptors. Some agonists of the imidazoline receptors reduce the binding of phencyclidine to NMDA receptors. This mechanism reduces the hallucinogenic effect of this substance [27]. The abstinence syndrome is the phenomenon that occurs when the administration of substances that have produced addiction is suddenly stopped but is not encountered in the case of hallucinogens. Agmatine significantly reduces the intensity of the withdrawal syndrome experimentally produced with naloxone in rodents who have received chronic morphine. This effect of agmatine is produced

by stimulating presynaptic I1 receptors and is independent of the action of agmatine on alpha 2 receptors. Clonidine also reduces the intensity of this syndrome by stimulating both presynaptic I1 receptors and by acting on alpha 2 receptors. Efaroxan (an antagonist of I1 receptors) significantly reduces the effect of agmatine in the withdrawal syndrome induced by naloxone [28].

Convulsions

Agmatine has an anticonvulsant effect. Agmatine has an anticonvulsant effect.

This biogenic amine reduced both experimentally induced convulsions with pentetrazol and those produced by electroshock. Agmatine (20–100 mg/kg intraperitoneally) increased the threshold of seizures induced by electroshock. In pentetrazol-induced convulsions, agmatine (100 mg/kg) increased the time between pentetrazol administration and the convulsion onset [29].

Stress

Different types of trauma are accompanied by significant post-traumatic stress disorders [30]. Administration of agmatine (40 μg/rat, ice) in an experimental stress model significantly reduced freezing time (the main indicator of the intensity of the stress response in this type of experiment). This action of agmatine is mediated by both I1 and I2 receptor stimulation because the administration of Moxonidine separately from 2-BFI has the same effect of reducing freezing time in rats. Mice exposed to experimental stress had a significantly increased serum corticosterone level and decreased in concentration of BDNF (brain-derived neurotrophic factor). Agmatine decreased the level of serum corticosterone and increased the concentration of BDNF. The levels of acetylcholinesterase and oxidative stress were also significantly reduced after administering this biologically active amine [31]. Existing experimental data show that the cerebral imidazoline system has a neuroprotective role in stress conditions. Stimulation of I1 and I2 receptors reduces cognitive decline, anxiety and depression caused by various stressors. BU224 (2.5 or 10 mg/kg) selectively blocks I2 receptors, causing an increase in corticosterone concentration. A normal level of cerebral agmatine is an important element in neuroprotection in chronic stress conditions.

Neurodegenerative diseases

Neurodegenerative diseases have an increasing frequency and prevalence at all ages, but especially in people over 65 years of age. Dementia and Huntington's disease are some of the most severe and difficult-to-treat psychiatric diseases. I1 receptor agonists improved motor and cognitive performance in animals with experimental models of Huntington's disease [32].

The imidazoline system is involved in improving the progression of some neurodegenerative diseases. In an experimental mouse model of Alzheimer's disease, administration of an I2 receptor synthesis agonist (LSL60101 1 mg/kg daily for four weeks) significantly improved cognitive and behavioral decline. Experimental data indicate that selective I2 receptor agonists improve the progression of Alzheimer's disease and increase therapeutic performance, and they could constitute a new therapeutic perspective in this disease [33].

Also, the association of this I2 agonist with donepezil increased the therapeutic effects of this drug [34]. LSL60101 treatments decreased the concentration and synthesis of amyloid-β40 and tau hyperphosphorylation. Figure 1 shows some implications of the imidazoline system in the pathogenesis of some neuropsychiatric diseases.

Hyperphagia

Some authors consider hyperphagia a disease, while others consider it only a symptom within some diseases. In rats experimentally induced with streptozotocin, stimulation of I1 receptors resulted in increased food intake and hyperphagic behavior [35].

Anxiety

Anxiety is an increasingly common problem in contemporary society. Sometimes declared and sometimes hidden, it affects a large number of people of all ages.

Experimental administration of agmatine (10–20 mg/kg, i.p.) to rats produced a significant reduction in anxiety. The anxiolytic effect of agmatine is produced by stimulating both I1 and I2 receptors. Separate administration of 2-BFI (I2 agonist) (0.25 mg/kg i.p.) and moxonidine (I1 agonist) also had anxiolytic effects. In states of anxiety as well as in major depression, agmatinase is overexpressed in the ventral hippocampus [36].

B. Some normal somatic activities of the brain

There are clear implications of this system in normal CNS activities, such as: normal memory; neuroprotection; some motor activities; water and salt ingestion; food ingestion.

The imidazoline system similarly influences the social behavior of humans and some animals.

Neuroprotection

The human brain is constantly under the action of factors with a harmful and destructive effect on both neurons and neuroglia. In some cases, there is a direct toxic effect that causes cellular damage and even the death of neurons and neuroglia, and in other cases, apoptosis is influenced. Neuroprotection is therefore an essential factor

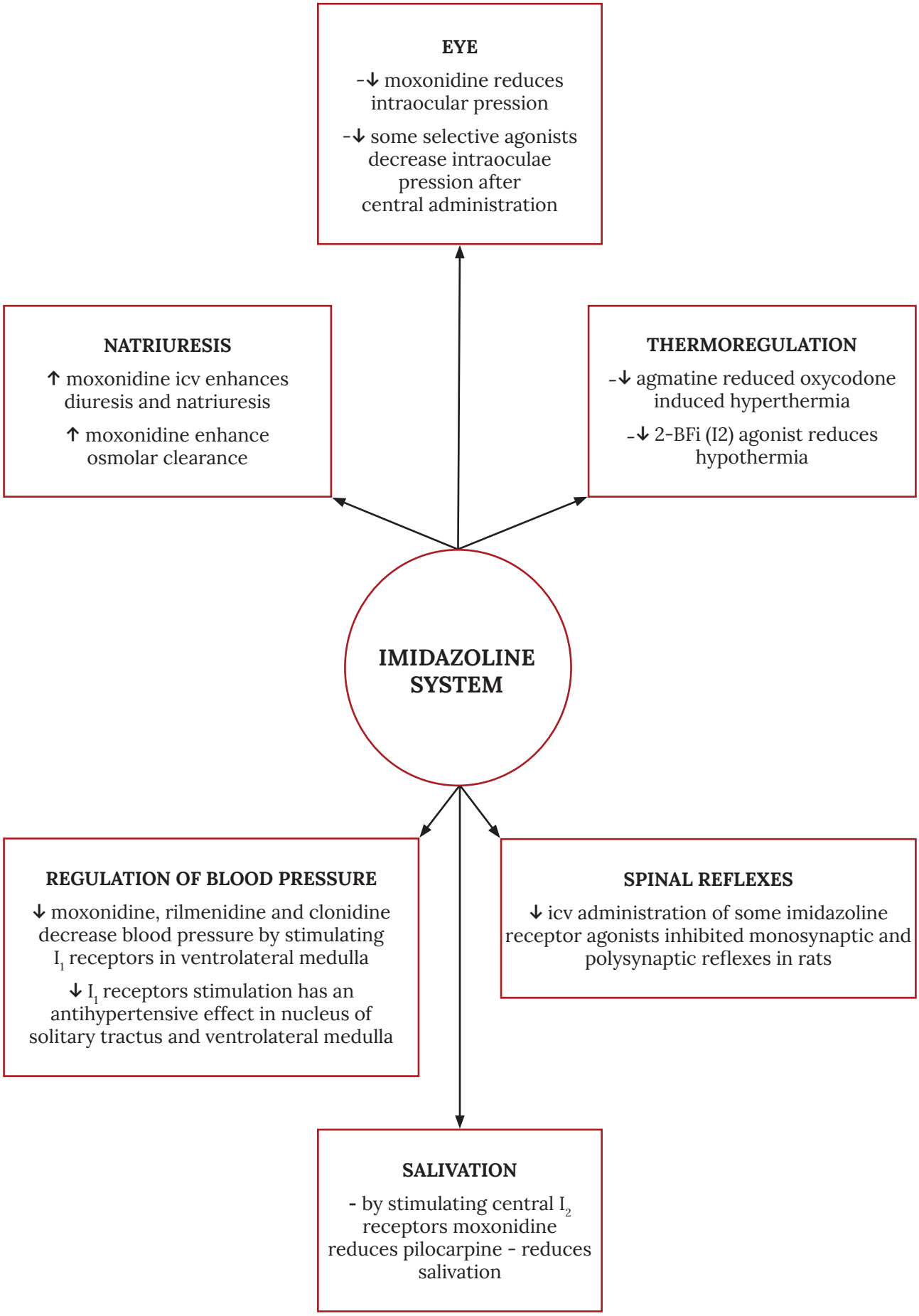

Figure 1. Central I_1/I_2 imidazoline receptors govern vasodepression, natriuresis–diuresis, ocular pressure, thermoregulation, spinal reflexes and salivary output.

for normal brain activity. Several factors are involved in neuroprotection, including the imidazoline system. Both I1 and I2 receptors are involved in neuroprotection but through different mechanisms of action.

One of the main mechanisms by which the imidazoline system is involved in neuroprotection is the action of I1 agonists (such as rilmenidine) to increase the stability of lysosomal membranes and reduce oxidative cytotoxicity in astrocytes [37, 38]. These experimental data open the perspective of using rilmenidine, moxonidine and possibly other selective I1 receptor agonists that can cross the blood-brain barrier not only for the treatment of hypertension and the prevention of stroke but also as neuroprotective factors in numerous pathological situations. Administration of the I2-imidazoline receptor ligand LSL 60101 prevented the death of motor neurons and determined a reactive astrocytosis [39]. Administration of 2-BFI significantly reduced experimental autoimmune encephalomyelitis-induced spinal cord injury. The mechanism of this protective effect was based on the increase in brain-creatine kinase (B-CK) activity, as well as CaATPase and the decrease in calpain activity [40].

In all cases, translating experimental data into clinical practice must be done cautiously, and clinical studies are absolutely necessary, but the existing results open new perspectives regarding neuroprotective therapy.

Vegetative functions of the central nervous system

There are also implications of the imidazoline system in the vegetative activities of the central nervous system.

Intraocular pressure

Moxonidine administered intracerebroventricularly in animals produces a decrease in intraocular pressure. This effect is mediated by stimulation of I1 receptors and is blocked by efaroxan [41]. At least part of the effect of moxonidine and rilmenidine (selective I1 agonists) is mediated by their action on central sympathetic structures because, after sympathectomy, this effect is suppressed [42]. Moxonidine also produces mydriasis. The central sympathetic is also involved in the production of this effect, but the participation of I1 receptors from the eye is not excluded. A major mechanism in the production of ocular hypotension after central administration of moxonidine is the increase in uveoscleral outflow. Existing experimental data suggest a possible implication of a decrease in the concentration of agmatine at the level of some central structures but also in the periphery in the appearance or worsening of some forms of glaucoma.

Diuresis and natriuresis

I1 receptors are also involved in natriuresis produced by a central mechanism. The ice. The administration of moxonidine increases not only natriuresis but also diuresis. This effect is produced by stimulating the sympathetic because denervation of the kidneys suppresses it [43].

Administration of moxonidine into the median septal area reduces pilocarpine-induced salivation. This effect is mediated by stimulation of I1 receptors and occurs by reducing central parasympathetic activity [44]. Central alpha 2 receptors are not involved in producing this effect of moxonidine.

Regulation of arterial pressure

The imidazoline system is involved in regulating arterial pressure both through central action and peripheral effects. Imidazoline receptors in the brainstem and pons are considered to be most involved in the regulation of vascular tone and blood pressure. I1 receptors are more involved in this action than I2 receptors. Rilmenidine and moxonidine (drugs with high selectivity for I1 receptors) lower blood pressure and have an antihypertensive effect [45]. The two drugs have both central and peripheral action, but the central action is the most important. Clonidine also reduces blood pressure through central action, but its effect is produced by stimulating both I1 receptors and central alpha 2 receptors [46, 47]. In the vasodepressor effect of I1 agonists, receptors in the ventrolateral medulla play an important role [48]. There are interrelationships between the eicosanoid system and the imidazoline system. Inhibition of cyclooxygenases reduces the vasodepressor effect of moxonidine. The interaction occurs both at the cerebral and peripheral levels because peripherally administered cyclooxygenase inhibitors and moxonidine cross the blood-brain barrier and interact inside and outside the brain.

Thermoregulation

The imidazoline system is also involved in thermoregulation. The existing data are few and still incompletely explained. By stimulating I1 (and probably also I2 receptors), Agmatine greatly reduces the hyperthermia produced by oxycodone. In high doses (10–50 mg/kg), this endogenous agonist of imidazoline receptors blocked the hyperthermic effect of morphine in rats. This action of agmatine is mediated by stimulation of I2 receptors (and perhaps in part also of alpha2 receptors) as it was blocked by idazoxan [49].

Clonidine, acting as an agonist of both I1 and alpha2 receptors, reduces both the hyperthermia caused by oxycodone and that caused by the administration of morphine. Agmatine and other I1 agonists administered to animals that have not previously received any other substance have no

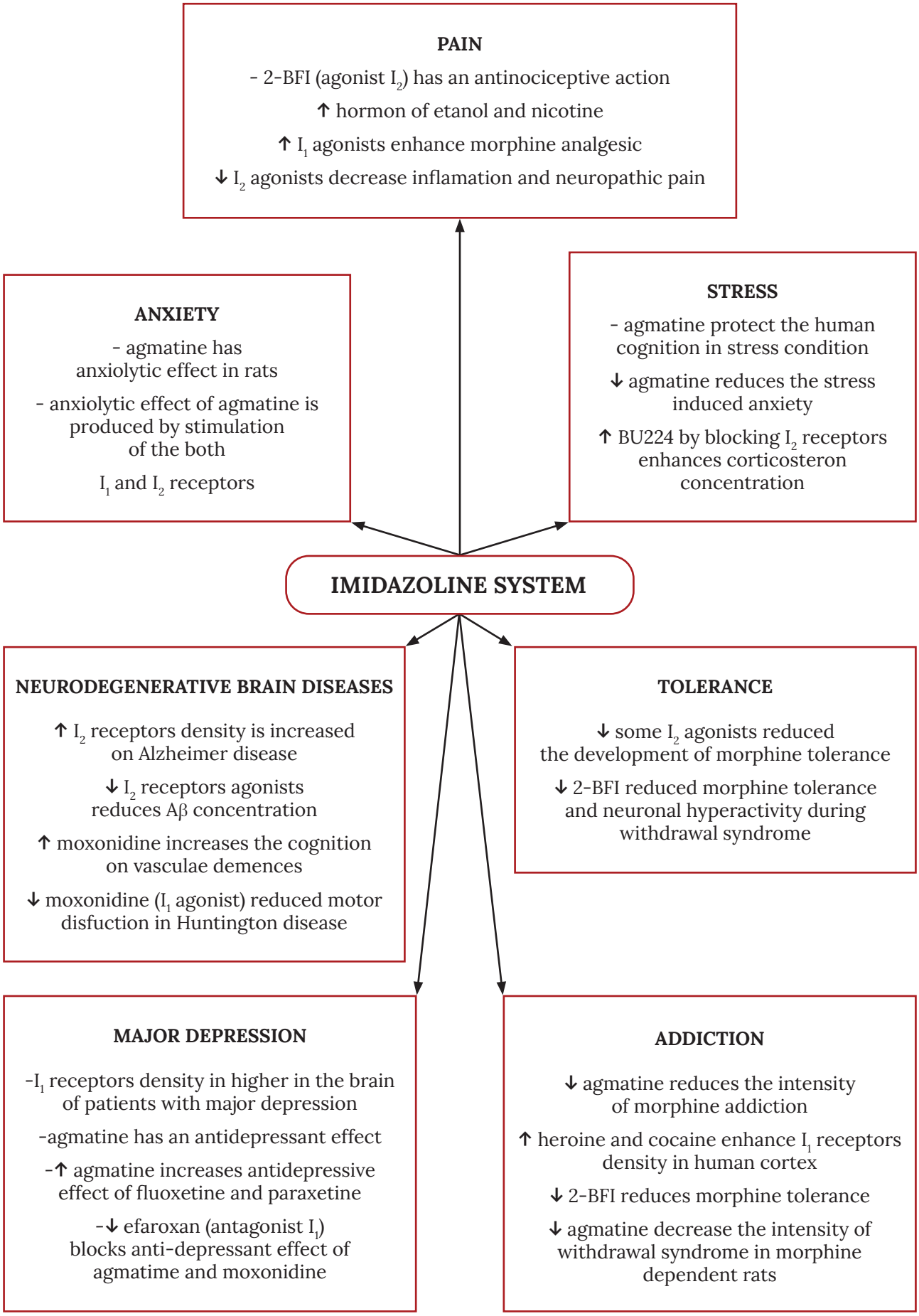

Figure 2. Imidazoline signalling attenuates pain, stress and mood disorders, slows neurodegeneration, and mitigates opioid tolerance and addiction.

hypothermic effect. I2 receptors are also involved in thermoregulation. Thus, 2-BFI (a selective agonist of I2 receptors) causes hypothermia [50].

Spinal reflexes

I2 receptors have a role in the modulation of spinal reflexes. Idazoxan by blocking I2 receptors, but also alpha2 potentiates spinal reflexes in the decerebrate rabbit. This effect is produced mostly by blocking I2 receptors at the level of monoamine oxidase (MAO) and possibly also by acting on some I2 receptors on the mitochondrial membrane and is completely independent of blocking the sites of MAO activity with pargyline or clorgyline [51]. Intracerebroventricular administration of tizanidine (an imidazoline receptor agonist) causes inhibition of monosynaptic and synaptic reflexes in non-spiralized rats. Tizanidine is a drug used in clinical practice in the treatment of spastic states [52]. It acts on I2 receptors, but some authors consider it an agonist of cerebral I3 receptors [53]. These authors argue that supraspinal imidazoline receptors are involved in modulating the activity of descending monoaminergic pathways in tizanidine-induced inhibition of rat spinal reflexes. However, the existence of cerebral I3 receptors remains controversial. The implications of the imidazoline system in autonomic brain functions are shown in Figure 2.

Therapeutic implications

Moxonidine, rilmenidine and clonidine are used to treat hypertension. Clinical data show a therapeutic effect of rilmenidine in diabetic neuropathy [54]. Rilmenidine monotherapy (1.42 mg/day for one year) in patients with left ventricular hypertrophy and hypertension reduced the left ventricular mass index [55]. A therapeutic target for the near future is the development of agmatinase inhibitors, which, according to existing data, would be useful in various pathological conditions in a large number of patients.

Conclusions

The imidazoline system is one of the essential autacoid systems for the human body, and it has vast implications at the cerebral level [56–58]. The role of this system in normal brain function and in the pathogenesis of various psychiatric and neurological diseases is only partially known. For some of the existing results, there is currently only experimental data without confirmation in human clinics. Clinical practice currently uses only I1 receptor agonists (moxonidine, rilmenidine and clonidine) and no I2 receptor agonists. There are a number of selective agonists of I1 and I2 receptors used experimentally, but for various reasons, they have not been introduced into clinical practice. It is necessary to produce substances with toxicity and pharmacokinetics adequate for their use as drugs in human clinics.

The serum concentration of agmatine should be determined in all cases of mood disorders, addiction, neurodegenerative diseases and convulsive states. A deficiency in this biogenic amine is likely involved to a greater or lesser extent in the pathogenesis of these pathological states. Since agmatine is partially synthesized in the human body but in a significant proportion introduced into the body through food intake, it is necessary to know and to recommend within the framework of nutritional medicine the constant use of those foods that provide a sufficient supply of agmatine. Between the imidazoline system and the other systems of endogenous active substances in the human brain, there are complex interactions that are little known today but essential for a detailed understanding of the functioning of the nervous system and of our organism in its complexity. Finally, understanding the complexity of the autacoid systems in the human body and how they interact with each other but also with the human genetic structure is an essential element for understanding genetic-epigenetic interactions, a fundamental element of life but also of our scientific medicine.

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Conflict of interest

The author declares no conflict of interest.

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