INVolVEMENT OF IMIDAZOLINE SYSTeM IN DRUG ADDICTION

Diana Ciubotariu, M. Nechifor
University of Medicine and Pharmacy “Grigore T. Popa” - Iasi
Faculty of Medicine
Discipline of Pharmacology

INVolVEMENT OF IMIDAZOLINE SYSTeM IN DRUG ADDICTION (Abstract): The imidazoline system (a concept which is barely over decades old) consists in imidazoline receptors I₁, I₂ and I₃ and their active endogenous ligands, the most important of which is agmatine. Brain contains both I₁ and I₂ of imidazoline receptors. One of the most important functions of this system is modulation of different behaviour components, such as suicidal behaviour, stress, anxiety, food intake etc. Own preliminary data revealed different effects of α₂ and imidazoline-receptors antagonists on morphine conditioned place preference (efaroxan reduces its intensity, while idazoxan has no influence); this reveals a possible different role of I₁ and I₂ receptors in reward system. Keywords: IMIDAZOLINE RECEPTORS, REWARD SYSTEM, DRUG ADDICTION

The concept of imidazoline brain system is only a few decades old. The imidazoline system consists in imidazoline receptors I₁, I₂ and I₃ and their active endogenous ligands, the most important of which is agmatine. Brain contains both I₁ and I₂ of imidazoline receptors. One of the most important natural agonists is agmatine (decarboxylation product of arginine). Identification of agmatine as an endogenous ligand for imidazoline receptor leads to important knowledge over imidazolinic system roles in the body (1). There is a particularly of the connections between imidazoline and adrenergic brain system, as certain imidazoline agonists and antagonists also act on α₁ and α₂ adrenergic receptors.

Existing evidence show the importance of imidazoline in modulating central nervous system functions. Existent data show that I₁ and I₂ receptors have different effects on some behavior components, such as suicidal behavior, stress, anxiety, food intake etc.

Imidazoline system is important for both normal and pathological behavior. Thus, changes in the imidazoline system balance have been detected certain neurological and especially psychiatric diseases.

REWARD SYSTEM

The biological mechanism and neural pathways mediating behavior motivated by events commonly associated with pleasure have been identified and described. These events are termed "rewards" and are viewed as primary factors governing normal behavior. The neural pathways involved in pleasure-mediated behavior are referred to as “brain reward system”. Main
rewards may be classified as natural (such as food, liquid intake, sex) and environmental (drugs of abuse, brain electrical stimulation of certain areas). The neuroanatomical elements of rewarding stimulation have been identified and ventral tegmental area, nucleus accumbens, ascending mesolimbic dopamine system, middle forebrain bundle are among the most important structures mediating reward. Dopamine is considered the most important neurotransmitter responsible for reward, but glutamate, serotonin, substance P, norepinephrine, endogenous opioids, GABA are also critically involved (2).

**SUBSTANCES ACTING ON IMIDAZOLINE RECEPTORS AND THEIR INFLUENCE ON REWARD-RELATED BEHAVIOR**

The imidazoline system has at least two important characteristics: some agonist and antagonists also act on the α-adrenergic system, and agmatine is synthesized from arginine, which is also a source of nitric oxide. There are I2 binding sites on monoamine oxidase (MAO) molecule, an essential enzyme for catecholamine metabolism. The fact that some agonists or antagonists of imidazoline receptors have also effect on α-adrenergic receptors or MAO also suggests certain interactions between imidazoline and adrenergic systems.

Imidazoline receptors have been identified in all brain areas; as to imidazoline system involvement in addictions, it is of special importance that this type of receptors is present in brain reward system cells (neurons and neuroglia). Experimental research on laboratory animals shows that agmatine influences some types of drugs addiction, most of them referring to opioid addiction. Clonidine (mainly known as α2-receptors agonist, but also I1-receptors agonist) is a very important agent used for withdrawal treatment. Agmatine itself has no reinforcing effect, but it determines a reduction in opioid dependence either systemically (intraperitoneally or subcutaneously) or centrally (intrathecally or intracerebroventricularly) (3). This effect is believed to be mediated by imidazoline I1-receptors (4).

Pretreatment with agmatine (40 or 80 mg/kg, intraperitoneally) significantly inhibited the acquisition of intravenous morphine self-administration as assessed by the nose-poke response and morphine intake. The mean number of days required to meet the acquisition criteria for intravenous morphine self-administration was significantly prolonged. After acquisition of intravenous morphine self-administration, chronic administration of agmatine (40 or 80 mg/kg x 30 days, bid, intraperitoneally) during the extinction period significantly prevents the re-acquisition of intravenous morphine self-administration. The ability of agmatine to inhibit the acquisition and re-acquisition of intravenous morphine self-administration suggests a possible use of agmatine in the treatment of opioid dependence (5).

Agmatine prevents tolerance to opioids analgesia either systemically (intra-peritoneally or subcutaneously) or centrally (intrathecally or intracerebro-ventricularly) (6) and reduces fentanyl self-administration (7). These facts can be of real therapeutic benefit, especially as numerous recent studies proved that I2-agonists, including agmatine, potentiate opioid-induced analgesia (8, 9, 10) Also, a very beneficial fact is reversion of morphine-induced memory impairment by agmatine, effect which is antagonized by idazoxan (I2 antagonist) (11).

Also, agmatine reduces the intensity of
morphine-induced conditioned place preference in mice (12) in a dose-dependent manner. Conditioned place preference is an experimental model investigating the rewarding effects of different stimuli, where the animal develops an association between the subjective states produced by the stimuli and the environmental factors associated to these stimuli.

There are also other addictive substances than opioids the behavioral effects of which are lowered by agmatine. Repeated agmatine treatment altered nicotine sensitization in mice (13).

Regarding the effects of psycho-stimulants on brain reward, several studies have also lead to relevant conclusions. Also, agmatine, at doses that did not produce place preference, aversion or altered motor activity significantly decreased the development of methamphetamine-induced place preference when agmatine was administered in combination with methamphetamine during place conditioning (14).

The specific I1 receptor agonist moxonidine reduces cue-induced reinstatement of cocaine-seeking behavior, suggesting that moxonidine might have substantial potential for treating addictive disorders (15).

Agmatine (5-20 mg/kg) significantly blocked ethanol (0.5 g/kg)-induced locomotor hyperactivity. These doses of agmatine did not affect the locomotor activity in naive mice when they were administered alone. Other results suggest that agmatine has an important role in ethanol-induced locomotor hyperactivity in mice. There may be a relationship between the addictive psychostimulant effects of ethanol and central agmatinergic system (16).

A theoretical rationale supports the fact that tizanidine (α2-adrenoceptor agonist that inhibits noradrenaline release and binds to imidazoline receptors) can be an effective treatment for alcohol withdrawal syndrome as well as for the prevention of relapses (17).

Our preliminary data revealed different effects of α2 and imidazoline-receptors antagonists on morphine conditioned place preference (efaroxan, 1mg/kg reduces its intensity, while idazoxan, 0.25mg/kg has no influence), while neither of these substances significantly modifies the intensity of opioid dependence in rats.

**DISCUSSION**

Based on the presented data referring to substances acting on imidazoline receptors and the way they modulate the reinforcing effects of some addictive substances, several hypotheses referring to the mechanisms by which imidazoline system modulates reward pathways have been formulated.

There are important functional connections between imidazoline system and other neuromediator systems involved in drug dependence. The most important functional connections in case of imidazolinic system are those with catecholaminergic system.

A first very important element of these connections is that some I1-receptor agonists (such as clonidine) are also α2-receptors agonists. Other substances which act as competitive I1-receptor antagonists (such as efaroxan) also act on adrenergic receptors.

The problem of imidazoline system involvement in addiction might also be connected with nitric oxide involvement in the mechanism of production of those dependences. Arginine (the amino acid which also serves for arginine precursor) is also the main source of nitric oxide. Among others, a possible involvement of inducible nitric oxide system has also been incriminated for...
agmatine effect of reducing morphine-induced conditioned place preference, as minoguanidine, a specific inducible NOS (nitric oxide synthase) inhibitor, significantly reduced the effect of agmatine (18). On the other hand, agmatine is a weak competitive inhibitor of neuronal NOS (9). It is known that morphine administration is followed by increased NO released, due to increased activity of constitutive NOS, but it decreases the activity of inducible NOS (via constitutive NOS-derived NO) (20, 21).

Agmatine, administered before morphine withdrawal determined a decrease of glutamate level in nucleus accumbens (a key element in reward mesolimbic dopaminergic pathways) in rats; also, agmatine acts as a NMDA-receptor antagonist (22, 23). Given the essential role of glutamate neurotransmission in brain reward system, these might serve as a reasonable explanation for the above-presented data related to agmatine capacity of reducing some aspects related to drug intake.

However, many aspects related to imidazoline-reward system interaction mechanisms are yet to be studied.

**CONCLUSIONS**

Imidazoline agonists determine inhibitory effects on several aspects related to the action of some drugs of abuse on reward-modulation pathways. Considering their potentiating effect on opioid analgesia and reversal of morphine-induced memory impairment, imidazoline agonists might represent valuable pharmacological agents for addiction treatment. Also, substances such as clonidine, which has been long used in withdrawal treatment, might due their beneficial effects in patients with opioid or alcohol withdrawal not only to imidazoline receptors blockade but also to adrenergic receptors blockade. Existent data are also opening the perspective of therapeutic use of other imidazoline system modulators.

Regunathan, 2006 (24) showed that agmatinase inhibitors (substances which blocks the enzyme which brakes-down agmatine) will offer a way to enhance agmatine brain concentration. This may be a useful in therapy to reduce the intensity of opioid addiction or even opioid withdrawal syndrome.

We believe that both imidazoline I1 and I2 agonists and antagonists might modulate reward system activity, this being of particular relevance for therapy.

Involvement of imidazoline system in behavior is surely a very fruitful study domain.

**REFERENCES**


22. Gibson DA, Harris BR, Rogers DT, Littleton JM. Radioligand binding studies reveal agmatine is a more selective antagonist for a polyamine-site on the NMDA receptor than arcaine or ifenprodil. *Brain Res* 2002; 952: 71-77.
