

Imidazoline Binding Sites

Key References

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Overview

Various compounds that possess an imidazoline or guanidinium moiety, along with a number of chemically related compounds, elicit a variety of pharmacological effects on cardiovascular/cerebrovascular function, metabolism, insulin secretion and ion transport. These compounds include the α_2 -adrenoceptor agonists clonidine, rilmenidine, moxonidine and guanabenz, the α_1 -adrenoceptor agonist/ α_2 -adrenoceptor antagonist cirazoline, the α_2 -adrenoceptor antagonist idazoxan, the ion transport inhibitor amiloride and other structurally related ligands. Although such ligands interact with known receptor systems, some of their functional effects, such as their centrally-mediated effects on blood pressure and their ability to augment glucose-induced insulin secretion from pancreatic β cells, are pharmacologically ill-defined. Indeed, several studies indicate that these molecules interact with distinct imidazoline binding sites. These sites share the common property of not recognizing endogenous agonists for known monoamine receptors and exhibiting high affinity for selected compounds containing an imidazoline, guanidinium or structurally-related substituent.

Radioligand binding and photo-affinity labeling studies indicate that imidazoline binding sites represent a heterogeneous family of proteins that are currently grouped as I₁ and I₂. The two groups of binding sites differ in their ligand recognition properties, tissue distribution and possibly their localization within the cell. I₁ binding sites have been associated with diacylglycerol or cAMP generation and are implicated in the centrally-mediated effects of imidazoline ligands on blood pressure. However, their primary structure has yet to be established and their precise functional

role remains controversial. Very recently, highly selective ligands for I₁ binding proteins, as compared with their activities at α_2 -adrenoceptors and I₂ binding sites, have been synthesized. These ligands include LNP 911, its radio iodinated analog-[¹²⁵I]-LNP 911 and the photo-affinity azido-derivative LNP 906. Binding studies using [¹²⁵I]-LNP 911 showed that this radioligand clearly discriminates I₁ binding sites from both I₂ binding sites and α_2 -adrenoceptors.

With respect to the I₂ subgroup of imidazoline binding proteins, evidence suggests that one member of this family is identical to the B isoform of the enzyme monoamine oxidase (MAO). However, the imidazoline binding domain on MAO is distinct from the enzyme active site that recognizes the mechanism-based inhibitors and it is not equally accessible in all tissues. At present, the role of I₂ binding sites in the regulation of MAO activity is still uncertain.

In addition to I₁ and I₂ imidazoline binding sites, a third site referred to as the I₃ site, has been reported in pancreatic β cells. The I₃ binding site displays ligand-recognition properties that differ from those of the other imidazoline binding proteins and appears to be involved in regulation of insulin secretion.

Current research in this area is also focused on the identification of putative endogenous ligands for imidazoline binding sites. Although agmatine was originally suggested as a potential candidate, subsequent studies have refuted these earlier claims. Specific endogenous β -carbolines have also been proposed as ligands for some imidazoline binding sites, which is of interest as earlier data in the literature suggested a role for β -carbolines as endogenous regula-

tors of MAO. More recently, it has been reported that imidazoleacetic acid-ribotide may be a potential endogenous ligand for I₁ and I₃ binding sites.

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CURRENTLY ACCEPTED NAME	I ₁	I ₂	I ₃
ALTERNATE NAMES	I ₁ Imidazole binding site I ₁ Imidazoline receptor	IGRS - imidazoline/guanidinium receptive site, non-adrenergic imidazoline-preferring binding sites, idaxozan (I) receptors	I ₃ Imidazoline receptor
LIGANDS	Clonidine (C7897), Cirazoline (C223), Benazoline (B4555), Moxonidine (M1559), Efaroxan (E3263), Benazoline (B4555), Rilmenidine (R134), LNP509, LNP911, LNP906, S23515, S23757	Cirazoline (C223), Amiloride (A7410) ^a , Guanabenz (G110), Metrazoline (M5685), Benazoline (B4555), Idazoxan (I6138), BU224 (B154), 2-BFI (RX 801077) ^a	Efaroxan (E3263), Idazoxan (I6138), RX871024, BL11282
PUTATIVE ENDOGENOUS LIGANDS	Agmatine (A7127), Harmane Imidazoleacetic acid-ribotide	Not known	Beta-carbolines Imidazoleacetic acid-ribotide
SIGNAL TRANSDUCTION MECHANISMS	DAG, cAMP	Possible regulation of MAO?	G protein Rhes K(ATP) channel
RADIOLIGANDS OF CHOICE	[³ H]-Clonidine, ^b [³ H]-p-Aminoclonidine, ^b [¹²⁵ I]-Iodoclonidine, ^b [¹²⁵ I]-LNP911	[³ H]-Idazoxan, ^{a,b} [³ H]-2-BFI, ^a [¹²⁵ I]-AMIPI, [¹²⁵ I]-AZIPI	Not known
TISSUE EXPRESSION	Brain, kidney, heart	Brain, kidney, liver, adipose tissue	Pancreatic β cells
PHYSIOLOGICAL FUNCTION	Sympathetic and cardiovascular functions control	Regulation of monoamine turnover	Stimulation of insulin secretion; glycaemia
DISEASE RELEVANCE	Hypertension, cardiac arrhythmias, congestive heart failure	Mood disorders	Type II diabetes

Abbreviations

[¹²⁵I]-AMIPI: 2-[3-Amino-4-[¹²⁵I]iodophenoxy]methyl imidazoline

[¹²⁵I]-AZIPI: 2-[3-Azido-4-[¹²⁵I]iodophenoxy]methyl imidazoline

2-BFI: 2-(2-Benzofuranyl)-2-imidazoline

BL11282: 5-Chloro-3-(4,5-dihydro-1H-imidazol-2-yl)-2-methylindole

BU224: 2-(4,5-Dihydroimidaz-2-yl)-quinoline

LNP 509: 2-(Dicyclopropylmethylamino)-4,5-dimethyl-pyrroline

LNP 911: 2-(2-Chloro-4-iodo-phenylamino)-5-methyl-pyrroline

LNP 906: (5-Azido-2-chloro-4-iodo-phenylamino)-5-methyl-pyrroline

RX871024: 2-(N-Phenyl-indoyl)imidazole hydrochloride

S23515: 2-Amino-5-(2-Bromo-phenoxy)methyl-oxazoline

S23757: 2-(2-Fluoro-5-methyl-phenyl)-imidazoline

FOOTNOTES

a The imidazoline binding domains on MAO-A and MAO-B exhibit distinct ligand recognition properties. Idazoxan, BU224 and 2-BFI exhibit higher affinity for the imidazoline binding domain on MAO-B. Amiloride exhibits higher affinity for the imidazoline binding domain on MAO-A. Nomenclature for subtypes of I₂ imidazoline binding sites is unresolved.

b For identification of imidazoline binding sites, these radioligands are commonly used in the presence of 10 μM rauwolscine or epinephrine to block binding to α₂-adrenoceptors.