

Imidazoline Binding Sites

Key References

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Overview

Various compounds with an imidazoline or guanidinium moiety elicit a number of pharmacological effects on metabolism, secretion, ion transport and cardiovascular/cerebrovascular function. These compounds include the α_1 -adrenoceptor agonist/ α_2 -adrenoceptor antagonist cirazoline, the α_2 -adrenoceptor antagonist idazoxan, the α_2 -adrenoceptor agonist guanabenz, 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 proteins. 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.

Although the synthetic ligands that are recognized by imidazoline binding proteins elicit several cell responses, the signaling pathways involved and the relative importance of these proteins in these events are unclear. Such entities may represent an actual receptor in the target cell, directly linked to various cell signaling proteins, or they may be involved in the metabolism or transport of such ligands across the cell membrane.

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 may be involved in diacylglycerol generation or cAMP generation and are implicated in the centrally-mediated effects of imidazoline ligands on blood pressure. However, their precise functional role is controversial and the primary structure of this entity is not established.

Two members of the I₂ subgroup of imidazoline binding proteins are identical to the A and B isoforms of monoamine oxidase (MAO). 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.

Additional areas of research in this field include the possible existence of imidazoline binding proteins distinct from the I₁ and I₂ subtypes and the identification of a putative endogenous ligand for imidazoline binding sites. The imidazoline binding site in pancreatic β cells may define an additional subtype of imidazoline binding sites and has been termed the I₃ site. Several laboratories have focused on the identification of endogenous ligands for this family of binding sites and although agmatine was originally suggested as such a ligand, subsequent studies indicated that this compound is not likely to be an endogenous ligand for these sites. More recently, it has been reported that specific endogenous β -carbolines exhibit relatively

high affinity for some imidazoline binding sites, which is of interest because of earlier data in the literature which suggest a role for β -carbolines as endogenous regulators of MAO.

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CURRENTLY ACCEPTED NAME	I ₁	I ₂
ALTERNATE NAMES	Imidazole binding site Imidazoline receptor	IGRS - imidazoline/guanidinium receptive site, non-adrenergic imidazoline-preferring binding sites, idazoxan (I) receptors
SELECTIVE LIGANDS	Clonidine (C 7897) Cirazoline (C-223) Benazoline (B 4555) Metrazoline (M 5685) Moxonidine (M 1559) Efaroxan (E 3263) Rilmenidine (R-134)	Cirazoline (C-223) Amiloride (A 7410) ^a Guanabenz (G-110) Metrazoline (M 5685) Benazoline (B 4555) BU224 (B-154) ^a 2-BFI (RX 801077) ^a
SIGNAL TRANSDUCTION MECHANISMS	Unknown, DAG ? cAMP ?	Unknown; possible regulation of monoamine oxidase ?
RADIOLIGANDS OF CHOICE	[³ H]-Clonidine ^b [³ H]- <i>p</i> -Aminoclonidine ^b [¹²⁵ I]-Iodoclonidine ^b	[³ H]-Idazoxan ^{a,b} [³ H]-2-BFI ^a [¹²⁵ I]-AMIPI [¹²⁵ I]-AZIPI

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

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

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 rauwolscline or epinephrine to block binding to α₂-adrenoceptors.