Imidazoline binding sites on receptors and enzymes: Emerging targets for novel antidepressant drugs?

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Clonidine, like many other imidazoline drugs, is usually thought of as a selective α_2-adrenergic agonist and is approved for use as a centrally acting antihypertensive agent. In addition, clonidine is prescribed off-label to treat some cases of Tourette's syndrome, and it may also have a role in the treatment of other psychiatric conditions, including obsessive–compulsive disorders, panic states, schizophrenia and affective disorders.[1–5] However, the finding by Bousquet et al[6] that clonidine also has high affinity for novel central nonadrenergic sites, and that binding to these sites contributes to clonidine's hypotensive efficacy, has cast doubt upon the simplistic theories based solely upon the activity of clonidine at α_2 receptors, and has led to the discovery and classification of novel imidazoline receptors and binding sites.[7] Indeed, evidence is growing that favours the involvement of some of these sites in the pathophysiology of depression and, thus, the possibility exists that drugs that modify imidazolinergic systems may be of use in treating depression and perhaps some other psychiatric and cardiovascular conditions.

Imidazoline binding sites have been subclassified into 3 major groups, based largely upon ligand selectivities and subcellular distribution.[7–10] Perhaps the pharmacology and physiology of imidazoline I_1 receptors (I_1R) are best understood, whereas the available data with respect to I_2 binding sites (I_2BS) are somewhat confusing. I_3 binding sites (I_3BS) were identified more recently and have consequently been studied less extensively. In the rostral ventrolateral medulla, I_1Rs are thought to act in concert with adrenergic receptors to exert central control over vascular tone.[11–13] Of more interest in the present context is the presence of similar I_1Rs in other brain areas and on the plasma membranes of platelets, which exhibit altered behaviour in several psychiatric disorders and normalize their behaviour following treatment with numerous therapeutics.[14] The cDNA for a human I_1R has recently been cloned,[15] and the expressed protein was homologous with murine nischarin,[16] which appears to be involved in cytoskeletal signalling.[17]

In human brain, I_1Rs are distributed in a regional manner, with the highest densities being found in the striatum, pallidum, gyrus dentatus of the hippocampus, amygdala and substantia nigra.[18] Receptor densities have been found to be different from controls in the brains of depressed subjects post mortem,[14] and numerous studies have also confirmed a marked elevation of platelet I_1R density in depressed patients, compared with control subjects.[19,20] Furthermore, following chronic treatment with desipramine,[19,20] fluoxetine,[19] citalopram, imipramine, clomipramine[21] or bupropion,[22] receptor densities were reduced toward control values. In the last study, the measured reductions in re-

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ceptor density correlated well with plasma bupropion concentration.[22] Although cluster analysis in patients receiving bupropion revealed no correlation between I_1R binding parameters and overall Hamilton Rating Scale for Depression scores,[23] alterations in receptor density did show a positive correlation with the retardation and melancholic symptoms associated with unipolar depression,[14] and Halaris and Piletz have raised the possibility that platelet I_1R density may represent a state marker for unipolar major depression.

None of the antidepressant agents used in the studies described above interact directly with I_1Rs at therapeutic concentrations, and it is thus presumed that alterations in receptor densities are secondary to some other effect induced by drug administration. However, the possibility that I_1R agonists such as clonidine and moxonidine might have antidepressant efficacy in their own right cannot be excluded. In the control of blood pressure at least, I_1R agonism may result in neuromodulation of adrenergic transmission.[13] Similar neuromodulation of adrenergic and serotonergic transmission in the limbic system might reasonably be expected to have an effect on mood: the potential neuromodulatory mechanisms of imidazoline ligands will be discussed further in this editorial.

Whereas a signal transduction system has been described for I_1Rs,[24,25] this is not, for the most part, the case for I_2BSs, and these sites are therefore not generally referred to as receptors. In fact, most I_2BSs described thus far appear to be binding sites on enzyme proteins.

In 1991, Tesson et al[26] determined that a portion of I_2BSs were located on the outer membrane of mitochondria and, shortly thereafter, it was realized that these sites were associated with the monoamine oxidase (MAO) enzyme protein.[27] A number of imidazoline compounds were able to inhibit MAO, albeit with moderate potency,[28] and treatment of animals with amine oxidase inhibitors caused a substantial reduction in I_2BS density in rat brain and liver.[29] Whereas inhibition has since been shown to result from binding at the active site,[30] a second, high-affinity imidazoline binding site on the MAO protein does exist that is distinct from the active site of the enzyme.[30–34] Furthermore, in MAO-knockout mice, these I_2BSs were lost when expression of MAO-B, but not MAO-A, was blocked.[34] In other species, including human beings and rats, the possibility that MAO-A also presents I_2BSs should not be ignored.[35] However, despite all the comparative pharmacologic studies that have been completed, modulation of enzyme activity as a result of ligands binding to I_2BSs on MAO has yet to be demonstrated. Nevertheless, the potential to alter MAO activities through a modulatory site on the enzyme has obvious relevance and rather interesting implications in the field of antidepressant drug discovery.

Any role for I_1Rs or I_2BSs in the pathophysiology of psychiatric conditions would necessarily implicate endogenous agonists for these sites. The first compound for which imidazoline agonistic activity could be demonstrated was agmatine,[36,37] formed by decarboxylation of arginine.[38] Agmatine has been shown to possess antidepressant efficacy in 2 rodent models of depression[39,40] and may also have analgesic (or antihyperalgesic),[41] anxiolytic,[42] anti-inflammatory,[43] antiproliferative[44] and neuroprotective[45] properties. However, in addition to actions mediated via binding to imidazoline sites, agmatine can also exert such diverse effects as inhibition of nitric oxide synthase (probably through agmatine aldehyde)[43] and blockade of *N*-methyl-D-aspartate receptors.[45] Thus, the ability of agmatine to alter the pathophysiology of numerous conditions does not confirm the involvement of imidazoline receptors.

Some endogenous indolamines and imidazoles, such as tryptamine and histamine, display micromolar affinities for I_2BSs in rats and rabbits[46] and are significantly more potent than agmatine in this regard. Interestingly, when tryptamine is involved along with an aldehyde in a Pictet–Spengler condensation reaction, the product is a β-carboline. Some of these hallucinogenic compounds can be detected in the human brain and have nanomolar affinities for I_1Rs and I_2BSs.[47] Indeed, the β-carboline harmane acts like clonidine to cause hypotension, probably through an agonistic action at central I_1Rs.[48] In addition to their established affinity for benzodiazepine receptors and for MAO,[49,50] several β-carbolines show efficacy in a rodent model of depression.[51]

Despite the fact that several compounds that occur endogenously also exhibit imidazolinergic efficacy, the identity, or identities, of the functional endogenous agonist(s) remains a matter of great debate.

It seems rather remarkable that a great many of the imidazoline ligands described thus far interact with MAO, either as substrates (tryptamine) or as inhibitors (β-carbolines, numerous synthetic ligands). It might be implied from such observations that some structural similarity exists between the MAO active site and the ligand-binding site on I_1Rs and I_2BSs. This contention is

supported by the fact that several other amine oxidases that are unrelated to MAO, but share several substrates and inhibitors with MAO, also bind numerous imidazoline ligands. For example, agmatine is a substrate for diamine oxidase (DAO)[52] and for semicarbazide-sensitive amine oxidase (SSAO).[53] Tryptamine is also a substrate for SSAO,[54] whereas several synthetic imidazoline ligands are inhibitors of DAO (unpublished results, 1999). Indeed, both clonidine and the diuretic drug amiloride are DAO inhibitors,[55] and amiloride was also the ligand of choice to discriminate between 2 subtypes of I_2BSs, I_2A, which displays high affinity, and I_2B, which displays low affinity toward this compound.[7] These and other observations led to the suggestion that several "subtypes" of imidazoline receptors or binding sites may actually correspond to the active sites of several amine oxidase enzymes.[52]

We further explored the reasons underlying the remarkable degree of crossrecognition that appeared to exist between the active sites of amine oxidase enzymes and the agonist binding site on I_1Rs, hypothesizing that one or more endogenous, perhaps previously undescribed, I_1R agonists were metabolized by one or more amine oxidase enzymes. It was found that chronic inhibition of MAO-A and MAO-B, combined with inhibition of SSAO, resulted in a downregulation of I_1Rs in rat brain.[53] Inhibition of either enzyme family alone was largely without effect on receptor density, and inhibition of DAO also appeared to be unimportant in this regard. It was concluded that at least one endogenous I_1R agonist was a substrate for both MAO and SSAO, and it was suggested that tryptamine, or a tryptamine-derived β-carboline, might represent a suitable candidate.

The potential role for tryptamine as an endogenous I_1R agonist has taken on added significance with the recent resurgence of interest in trace amines. Tryptamine is a member of this small group of endogenous amines, which includes β-phenylethylamine, several tyramines and octopamine, and it has been suggested that alterations in the metabolism or function of at least some of these amines may be involved in the etiology of depression and in the mechanism of action of some antidepressant drugs.[56–58] It has long been argued that trace amines act as neuromodulators,[59–62] but a paucity of information regarding their target receptors and an inability of most groups to demonstrate functional effects of trace amines at physiologically relevant concentrations has resulted in a lack of progress in this area. However, the recent identification of a large family of G-protein-coupled trace amine receptors, including several human isoforms,[63] has stimulated research into the neurobiology of trace amines. Activation of expressed trace amine receptors, measured as increased cyclic adenosine monophosphate production, has been observed with trace amines and with several I_1R or I_2BS ligands, including clonidine, idazoxan, oxymetazoline and naphazoline.[64] Thus, based simply upon observations of common ligands, including common agonists, as well as apparent similarities in mechanism and outcome of stimulation, it seems plausible that some trace amine receptors and some imidazoline receptors are synonymous. Accordingly, it is reasonable to speculate that I_1R agonists may possess antidepressant efficacy through an ability to modulate biogenic amine neurotransmission in the limbic system. Alterations in concentrations of endogenous agonists, through inhibition of MAO and SSAO, and subsequent changes in receptors mediating neuromodulation,[53] would thus be expected to alter biogenic amine signalling. Several MAO inhibitor antidepressant compounds such as phenelzine and tranylcypromine and perhaps moclobemide[65] also inhibit SSAO to varying degrees. Whether or not alterations in imidazolinergic or trace aminergic neuromodulation contribute to the antidepressant efficacy of these drugs is still unclear.

The question remains to be answered as to why a high-affinity imidazoline binding site, separate from the active site, exists on MAO. Whereas some enzymes possess functions unrelated to their enzyme activity,[66] MAO is not known to take part in processes unrelated to amine oxidation. Thus, one may only presume that if binding of a ligand to the high-affinity I_2BS on MAO is able to elicit a physiologic response, then this should be reflected in some change in enzyme activity.

It has also been suggested that an imidazoline site may exist on bovine plasma amine oxidase, a soluble SSAO enzyme,[28] although it is not clear that the site in that particular case was distinct from the active site. Following acute inhibition in vivo of SSAO in rats, MAO-A activity in brown adipose tissue was elevated by around 500% within 2 hours of drug administration to the animals.[67] The SSAO inhibitors used in those studies had no stimulatory effect in vitro versus MAO-A, implying that a substrate for SSAO may have been responsible for the effect seen. Conversely, inhibition in vivo of MAO isoforms by tranylcypromine increased SSAO activity in the rat heart.[68] Furthermore, human

platelet MAO and rat brain MAO can be activated by a component of human plasma,[69,70] and human lung SSAO is also activated by plasma extracts.[71] Such observations seem to suggest that amine oxidase activities may be susceptible to endogenous modulation, presumably through binding of modulators to sites separate from the active sites of the enzymes. Thus, any inhibition of MAO activity by imidazoline compounds acting at such a site would only be apparent in the presence of an activator acting through the same site, and these conditions have not yet been satisfied during previous attempts to show effects of low concentrations of imidazoline compounds on MAO activities.

Although much remains to be done to elucidate the reason for the presence of an imidazoline site on MAO, all of the above speculation can be supported somewhat by recent results from our laboratory, which reveal an ability of some imidazoline ligands to stimulate SSAO activity in vitro, most likely through binding to a modulatory site on the enzyme (unpublished data, 2003). These findings raise the possibility of 2-way feedback between MAO and SSAO, perhaps mediated by trace amines, resulting in mutual regulation of enzyme activities. Research continues in our laboratory to examine the processes involved, with a view to discovering novel antidepressant drug candidates that may inhibit MAO in a noncompetitive manner with respect to amine substrate and that may open up interesting new possibilities for tissue-specific MAO inhibition.

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