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Role of Imidazoline-preferring Receptors in the Genesis of Epinephrine-induced Arrhythmias in Halothane-anesthetized Dogs

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Background: **Drugs with a central α_2-adrenergic action can increase the threshold for halothane–epinephrine-induced arrhythmias. Recently, imidazoline-preferring receptors were shown to play a significant role in the hypotensive effect of α_2-adrenergic agonists containing an imidazole ring in their structure. To address the question of whether the antiarrhythmic property of the α_2-adrenergic agonists was caused by activation of α_2-adrenoceptors or imidazoline-preferring receptors in the central nervous system, the effect of an imidazoline (atipamezole) and a nonimidazoline (L-659,066 and yohimbine) α_2-adrenergic antagonist were examined as etiologic factors in the genesis of halothane–epinephrine-induced arrhythmias in dogs.**

Methods: **Adult mongrel dogs were anesthetized with halothane (1.3%) and monitored continuously for systemic arterial pressure and for premature ventricular contractions. The arrhythmogenic dose (AD) of epinephrine, defined as the smallest dose producing four or more premature ventricular contractions within a 15-s period, was determined in the presence of atipamezole (an imidazoline compound that crosses the blood–brain barrier), L-659,066 (a nonimidazoline compound that does not penetrate the blood–brain barrier), and yohimbine (a nonimidazoline compound that passes the blood–brain barrier). These drugs were administered either intravenously or into the cisterna magna to assess the site of action for changes in responsiveness.**

Results: **Intravenous atipamezole decreased the AD of epinephrine in the dose-dependent fashion. However, neither L-659,066 nor yohimbine, administered peripherally, decreased the AD of epinephrine. Central administration of atipamezole also decreased the AD of epinephrine, while L-659,066, even if administered centrally, did not affect the AD of epinephrine in the presence of halothane.**

Conclusions: **Because the imidazoline ring-containing α_2-adrenergic antagonist (atipamezole) potentiated the halothane–epinephrine-induced arrhythmias and the nonimidazole α_2-adrenergic antagonist (L-659,066 and yohimbine) did not, it is possible that the imidazoline-preferring, rather than the α_2-adrenergic, receptor is responsible for the antiarrhythmic property of α_2-adrenergic agonists. (Key words: Anesthetics, volatile: halothane. Heart: arrhythmias. Receptors: α_2-adrenergic; imidazoline preferring. Sympathetic nervous system: α_2 antagonist; atipamezole; catecholamine; epinephrine; L-659,066.)**

α_2-ADRENOCEPTORS are distributed widely throughout the central nervous system and play a significant role in the regulation of several physiologic processes.[1] Previously, we reported that dexmedetomidine, a highly selective α_2-adrenergic agonist, increased the threshold for the development of halothane–epinephrine-induced arrhythmias through a central action.[2] Indeed, halothane–epinephrine-induced arrhythmias are but one of several types of arrhythmias that are modulated by central α_2-adrenergic action.[3]

Both functional and radioligand binding studies indicate the existence of another class of receptors or binding sites that resemble the α_2-adrenoceptors. These sites bind selectively α_2-adrenergic ligands that are either imidazoline (*e.g.*, clonidine or idazoxan) or oxazolines (*e.g.*, rilmenidine) but have a low affinity for agonists or antagonists without the imidazoline or oxazoline structure, such as epinephrine and yohim-

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