AH-1058:
A Novel Cardioselective Ca\(^{2+}\) Channel Blocker

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ABSTRACT

The pharmacologic profile of a cyproheptadine-related compound, 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-[(E)-3-(3-methoxy-2-nitro)phenyl-2-propenyl]piperidine hydrochloride (AH-1058), was assessed in various in vivo and in vitro models. In guinea pig cardiomyocytes, AH-1058 effectively suppressed L-type Ca\(^{2+}\) channel currents without affecting other ion channel or ion exchange currents. In rat cerebral cortical membranes AH-1058 appears to bind preferentially to L-type Ca\(^{2+}\) channels at phenylalkylamine- and benzothiazepine-binding sites. In canine isolated, blood-perfused heart preparations, AH-1058 exerted negative inotropic, dromotropic, and chronotropic and weak coronary vasodilator effects. In halothane-anesthetized dogs, AH-1058 suppressed ventricular contractility and decreased blood pressure and cardiac output. Total peripheral vascular resistance was hardly affected by the drug, suggesting that in vivo AH-1058 can selectively suppress cardiac, as compared to peripheral vascular, function. In conscious dogs, by intravenous administration AH-1058 reduced systolic blood pressure and maximal upstroke velocity of the left ventricular pressure, while it increased heart rate in a dose-dependent manner. The drug did not affect diastolic blood pressure, which is quite different from cardiovascular properties of well-known Ca\(^{2+}\) channel blockers, verapamil and diltiazem. This unique cardiovascular profile of AH-1058 is expected to be useful in the treatment of certain pathological processes such as the obstructive hypertrophic cardiomyopathy, vasovagal syncope, dissecting aortic aneurysm, and ventricular arrhythmias, in which selective inhibition of the ventricular Ca\(^{2+}\) channels is essential for drug therapy.