Title: HALOTHANE DECREASES SPECIFIC BINDING OF CALCIUM CHANNEL BLOCKER TO CARDIAC MEMBRANES.

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Introduction. Voltage dependent Ca++ channels in the cardiac plasma membrane allow the entry of Ca++ into the cardiac cell to initiate the Ca++ cascade leading to contraction. Recent evidence has suggested that one likely mechanism by which the volatile anesthetics depress cardiac contractility is by interfering with the influx of Ca++ through these channels during depolarization.\(^1\),\(^2\) A radiolabeled ligand, tritiated nitrendipine (\(^3\)HN), belonging to the class of drugs termed "calcium channel blockers" is now available. We have used H\(^3\)N, a dihydropyridine analog of the clinically available Ca++ channel blocker, nifedipine (NIF), as a probe to investigate the interaction of volatile anesthetics with the cardiac calcium channel. Data is presented which demonstrates the ability of halothane to decrease the binding of \(^3\)HN.

Methods. Rat cardiac membranes (CM) were prepared in 50mM Tris HCl pH 7.7 by a modification of the method of Murphy and Snyder. CM, H\(^3\)N, and halothane were incubated at 25°C for 45 minutes with and without 10\(^-6\)M nifedipine in Teflon\(^\circ\) lined vials.\(^6\) The incubation was stopped by vacuum filtration of the reaction mixture onto Whatman GF/C glass fiber filters. The filters were washed with 20ml of cold buffer; the \(^3\)HN retained on the filter was quantitated by liquid scintillation counting. \(^3\)HN binding to CM in the presence of NIF was considered non-specific binding, i.e. unrelated to the labeling of Ca++ channels. Ca++ channel specific binding was calculated as the difference between total binding and non-specific binding.

Results. The figure demonstrates the effect of halothane on the binding of \(^3\)HN to CM. The non-specific binding (open circles) was essentially unchanged by halothane, however, total binding (closed circles) was markedly decreased over the range of 0 - 2% halothane. This decrease in binding can all be attributed to a decrease in specific binding of \(^3\)HN to CM. In two separate preparations to CM's, 1.97% halothane decreased specific binding of \(^3\)HN by 64%.

Conclusion. The strength of cardiac muscle contraction can be modified by altering the amount of Ca++ that enters the myocardial cell during depolarization. Ca++ channel blockers are negative inotropic drugs because they interfere with the influx of Ca++ that enters the myocardial cell during depolarization. Halothane is a known myocardial depressant whose mechanism of depression is believed to be related to interference with one or more of the Ca++ sensitive sites in the myocardial cell. Recent electrophysiologic experiments from two separate laboratories have shown clear decreases in the slow Ca++ current in the SA nodal and papillary muscle cells. The data which we present in this communication gives biochemical support to the hypothesis that halothane depresses myocardial contractility by interfering with the function of the calcium channel.

References.