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The Effects of Haloperidol On Ouabain Cardiac Inotropy and Toxicity (40169)

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Various substances have been implicated as playing a role in the development of the inotropic and/or toxic effects of ouabain on the heart. Some of these, such as norepinephrine, have been directly involved (1) while others such as dopamine (2), histamine (3) and serotonin (4, 5) mimic some or all of the effects of ouabain.

It is known that dopamine is present in the heart (6) and has cardiac effects (2) but whether dopamine plays a direct role in heart function is unknown. In vagotomized dog hearts, haloperidol, a dopamine antagonist, has been shown to produce a negative chronotropic effect when injected in the sinus node artery (7). In these experiments haloperidol also inhibited the positive chronotropic effect of dopamine and norepinephrine. Other studies indicate that haloperidol is a potent dopamine antagonist in the brain (8). Little information is available as to the effect of haloperidol on cardiac muscle, nor is there any information on the effects of haloperidol on ouabain inotropy or toxicity in the heart. Since there is evidence in the central nervous system that ouabain increases brain dopamine levels in both depressant (9) and excitant doses (10), it seemed reasonable to investigate the effects of haloperidol on cardiac muscle with respect to ouabain inotropy and toxicity.

Studies with a variety of other blocking agents were also performed to compare the effectiveness of these agents to haloperidol in preventing ouabain toxicity in dose ranges known to block specific receptors. These drugs were chosen because of the following blocking actions: Metiamide blocks the H2 receptor, verapamil supposedly blocks "slow channel" calcium influx, propranolol blocks the beta receptor, methysergide blocks the serotonin receptor, chlorpromazine, triflorpromazine, and fluphenazine are phenothiazines which are α-adrenergic blocking agents, atarax is a drug with a variety of blocking actions (adrenergic, histamine, serotonin and acetylcholine).

Materials and methods. New Zealand rabbits (1-2 kg) were sacrificed by a sharp blow to the head and exsanguinated by cutting the carotid artery. The hearts were removed rapidly and placed in oxygenated (95% 0_2–5% CO_2) bicarbonate Ringers at pH 7.4.

The atria were divided into right and left sides and suspended in 70 ml of Ringers' by means of atrial clips. Ringers' solution having the following composition was utilized (mmolar): NaCl, 154; KCl, 5.4; glucose, 11; $NaHCO_3$, 6.0 and $CaCl_2$, 2.4. The left atria were driven by platinum field electrodes at 20% above threshold voltage, 2 Hz and 6 msec duration.

Resting tension was adjusted to 1.0 g and the temperature maintained at 30° ± 1°. Contractile force was measured using a FT03C Grass force displacement transducer.

The following drugs were used: haloperidol (Haldol), methysergide (Sansert), metiamide (SK&F #92058), ouabain, chlorpromazine (Thorazine), hydroxyzine HCl (Atarax), fluphenazine 2HCl (Prolixin), propranolol HCl (Inderal), triflupromazine HCl (Vesprin), and verapamil. All drugs were dissolved in distilled water. The total volume of drug solution added to the bath medium never exceeded 1 ml.

Ouabain toxicity was determined by the appearance of arrhythmias and/or a decrease in systolic tension and an increase in diastolic tension.

In vivo experiments were performed on rabbits anesthetized with 40 mg/kg pentobarbitol. Ouabain and haloperidol were dissolved in physiologic saline and water respectively, and administered through cannulation of the jugular vein. Cannula were heparinized and saline was used as a wash. The EKG was recorded on a Beckman R411 dynograph

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with type 9806A AC/DC coupler. A lead III electrocardiogram was taken.

Results. Initial experiments in isolated rabbit atria determined that 8×10^{-7} *M* was the highest effective inotropic dose of ouabain that did not produce toxicity in 60 min. Subsequent experiments using 1.6×10^{-6} *M* ouabain showed that mean time for toxicity to develop in spontaneous atria was 30.74 ± 1.98 (SEM) minutes ($n = 25$). Figure 1 shows the effects of various drugs on toxicity time of ouabain. Although triflupromazine, fluphenazine, methysergide and hydroxyzine–HCl showed effectiveness in increasing the time to toxicity, only haloperidol completely prevented toxicity at the concentrations tested. Note that propranolol was similar to haloperidol in prolonging toxicity time at 5×10^{-6} *M*. In separate dose response experiments comparing propranolol and haloperidol, haloperidol significantly prolonged toxicity time to ouabain at 1×10^{-6} *M* ($p < 0.02$) and 2.5×10^{-6} *M* ($p < 0.01$) (Fig. 2). Propranolol was not effective at these concentrations but was effective at 5×10^{-6} *M* (Fig. 1). Experiments with haloperidol and propranolol in spontaneous atria were stopped after 120 min if toxicity did not appear. Alone, haloperidol had a dose dependent negative chronotropic effect *in vitro* (Fig. 3) when compared to non-treated controls.

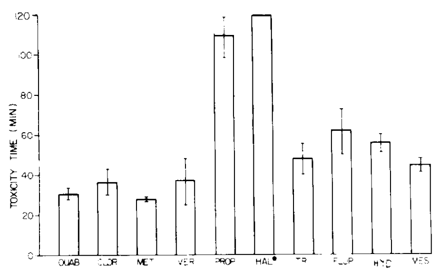

FIG. 1. The mean time to the onset of ouabain (1.6×10^{-6} *M*) toxicity ($n = 25$) is compared in spontaneous atria with atria pretreated for 30 min with chlorpromazine @ 5×10^{-7} *M* ($n = 5$), metiamide @ 1×10^{-5} *M* ($n = 3$), verapamil @ 1×10^{-7} *M* ($n = 3$), propranolol @ 5×10^{-6} *M* ($n = 6$), haloperidol @ 2.5×10^{-6} *M* ($n = 11$), triflupromazine HCl@ 1×10^{-6} *M* ($n = 4$), fluphenazine HCl @ 2×10^{-6} *M*, ($n = 4$) hydroxyzine HCl @ 2×10^{-6} ($n = 6$) and methysergide @ 1×10^{-5} *M* ($n = 4$) respectively. The bar heights represent mean time to toxicity ± SEM.

* Indicates that the experiments were stopped without appearance of toxicity.

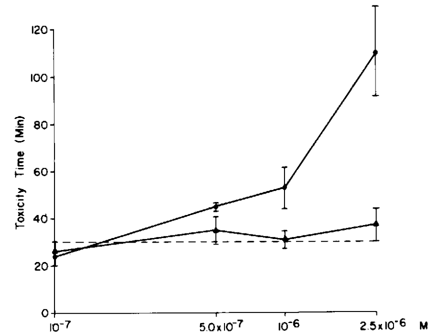

FIG. 2. Effect of propranolol (▲——▲) and haloperidol (●——●) at four different doses on toxicity time of ouabain @ 1.6×10^{-6} *M* ($n = 25$) (-----) in spontaneous atria. Both drugs were added 20 min prior to ouabain addition. All points are $n = 4$ except at 2.5×10^{-6} *M* where $n = 5$ for both drugs. Haloperidol treated atria (@2.5×10^{-6}) did not display toxicity except in one case (toxic at 43 min), all other atria were allowed to run for 120 min or longer.

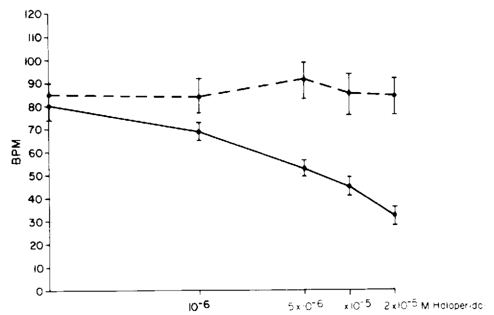

FIG. 3. The effects of cumulative increasing doses of haloperidol on heart rate in spontaneously beating right atria (●——●) and non-treated controls (●-----●). Each point is the mean of 6 experiments ± SEM. Intervals between doses is 1 hr.

Effects of haloperidol on ouabain toxicity and inotropy. At 2.5×10^{-6} *M*, haloperidol protects against toxic changes in both tension and arrhythmias (Fig. 4). The positive inotropic effect of ouabain however was not effected by haloperidol (Table I). When severe toxicity to ouabain was allowed to develop, the administration of haloperidol (2.5×10^{-6} *M*) completely reversed the toxicity (Fig. 5) in all cases studied ($n = 5$). Haloperidol ($n = 6$) also completely prevents the toxic effects of ouabain on contractility in driven atria (2 Hz), (stopped at 120 min) when compared to the driven ouabain treated controls ($n = 24$) (toxicity beginning at 44.24 ± 4.45 min (SEM)).

In vivo effects of haloperidol on ouabain *toxicity*. Response to cumulative ouabain increments of 0.025 mg/kg in 10-min intervals showed that at 0.150 mg/kg cardiac arrhythmias appeared on the EKG in anesthesized rabbits and 0.213 ± 0.0105 mg/kg produced death ($n = 6$). In other experiments, haloperidol (0.30 mg/kg) + ouabain (0.15 mg/kg) was compared with ouabain (0.15 mg/kg) control over a 15 min-period (Fig. 6). Haloperidol prevented completely or significantly reduced the arryhthmias associated with ouabain ($p < 0.001$, analysis of variance).

Discussion. The results of these studies showed that haloperidol is an effective inhibitor of ouabain toxicity (Figs. 1, 2, 4) and does not effect the positive inotropic action of ouabain on isolated rabbit atria (Table I).

The mechanism(s) by which haloperidol prevents ouabain toxicity is not clear from these studies. Since haloperidol produces a negative chronotropic effect (Fig. 3), it is

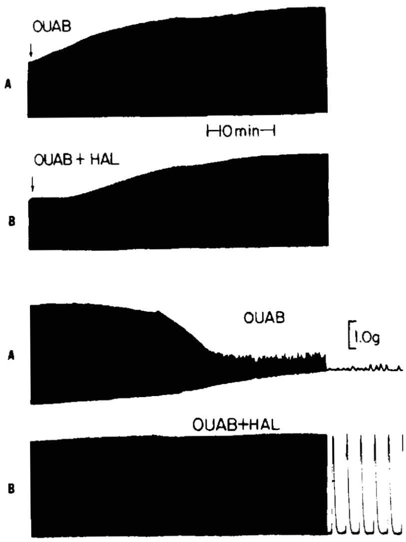

FIG. 4. Typical experiment showing the effect of haloperidol (2.5×10^{-6} *M*) on ouabain (1.6×10^{-6} *M*) toxicity. Upper two figures show the first 30 min of the experiment after the addition of drugs. The lower two figures show the continuation of the same tracings. A slow recording (0.05 mm/sec) and a fast recording (5 mm/sec) is shown in the lower two tracings.

TABLE I. EFFECT OF HALOPERIDOL ON THE INOTROPY OF OUABAIN IN SPONTANEOUS ATRIA.[a]

Treatment	Concentration	% Tension increase[b]
Ouabain ($n = 6$)	4×10^{-7} M	14.67 ± 1.32
Ouabain + Haloperidol ($n = 6$)[c]	4×10^{-7} M, 2.5×10^{-6} M	14.75 ± 1.83
Ouabain ($n = 8$)	6×10^{-7} *M*	24.67 ± 3.59
Ouabain + Haloperidol ($n = 8$)[c]	6×10^{-7} *M*, 2.5×10^{-6} *M*	25.47 ± 1.86

[a] Values are mean ± SEM.
[b] Tension measured 60 min following the addition of ouabain.
[c] Haloperidol added 20 min prior to ouabain.

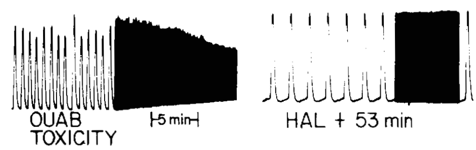

FIG. 5. A typical experiment showing ouabain (1.6×10^{-6} *M*) toxicity in the spontaneously beating right atrium and the reversal of toxicity with haloperidol (2.5×10^{-6} *M*) shown after 53 minutes in the same preparation. A slow (0.05 mm/sec) and a fast (5.0 mm/sec) recording is shown.

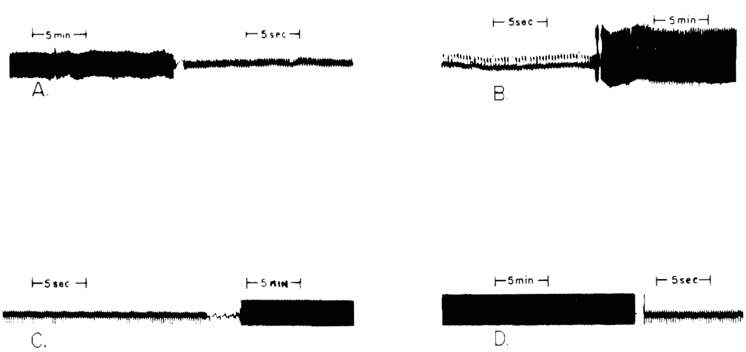

FIG. 6. ECG recordings (lead III) of anesthesized rabbits showing: A. Pretreatment strip of control, B. Same strip as A, 15 min after Ouabain (0.15 mg/kg), C. Pretreatment strip of control and D. Same strip as C, 15 min after haloperidol (0.30 mg/kg) + ouabain (0.15 mg/kg). A slow (50 mm/min) and a fast recording (5 min/sec) is shown.

possible that the effects of haloperidol on ouabain toxicity could be the result of the decrease in heart rate. This would seem unlikely, however, since haloperidol prevents ouabain toxicity in preparations stimulated at a constant rate. (See Results)

The effect of haloperidol could also be explained on inhibition of ouabain uptake so that toxic levels are not reached. This also appears unlikely since haloperidol completely reverses established ouabain toxicity (Fig. 5).

In addition, experiments in anesthetized rabbits show that haloperidol also prevents ouabain toxicity *in vivo* (Fig. 6).

Haloperidol could exert at least part of its effect on ouabain toxicity by a dopamine blocking action. However, it is known that the cardiac effect of dopamine can be blocked by β-adrenergic blocking agents and that haloperidol has a variety of effects other than blocking dopamine (7). It is planned to examine these possibilities in detail. A variety of other drugs were used in concentrations known to block slow channel Ca influx, the H-2, serotonin, and alpha adrenergic receptor (Fig. 1). In concentrations used none of these drugs were as effective as haloperidol and propranolol. Although it is possible that higher concentrations of these drugs may have been more effective, it suggests that the specific action blocked (slow Ca influx, H-2 receptor etc.) is not singularly involved in ouabain toxicity. Furthermore since haloperidol doesn't effect ouabain inotropism (Table I), it would appear that ouabain's inotropic effect is not mediated by stimulation of dopamine receptors or dopamine release.

Since both electrolytes and Na^+-K^+ATPase have been implicated in ouabain toxicity, it is possible that haloperidol exerts its effects by altering cardiac electrolytes (K^+, Na^+, Ca^{2+}) or by effecting the binding of ouabain to Na^+-K^+ATPase. We are currently studying these possibilities.

The main purpose of this paper is to show that haloperidol is extremely effective in preventing and reversing ouabain toxicity without inhibiting its inotropic effect. Thus haloperidol may be useful experimentally in separating and studying the therapeutic and toxic effects of ouabain. In addition, haloperidol or similar compounds may be useful agents in the clinical treatment of digitalis toxicity. Of particular interest is the fact that haloperidol was more effective in preventing ouabain toxicity in lower concentrations than propranolol (Figs. 1 and 2), a drug with known usefulness in treating cardiac arrhythmias due to digitalis toxicity (11). Additional studies should be carried out to determine if haloperidol is effective against other arrhythmics.

Since ouabain has a positive chronotropic effect (12) which is masked during toxicity and since haloperidol, a known dopamine blocking agent, inhibits ouabain toxicity and has a dose-related negative chronotropic effect both *in vitro* (Fig. 3) and *in vivo* (7), it seems possible that dopamine may play an important role in cardiac chronotrophism and ouabain toxicity.

Summary. Haloperidol, a dopamine blocking agent, has been shown to be effective in preventing and reversing ouabain toxicity *in vitro* and *in vivo* without inhibiting its inotropic action. Haloperidol may be useful experimentally in studying digitalis action and clinically in treating digitalis toxicity. Dopamine may play an important role in cardiac chronotrophism and ouabain toxicity.

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