The Effects of Cocaine and Lidocaine on Ouabain-induced Arrhythmias and on the Uptake of ^{3}H-ouabain in Guinea Pig Ventricle Strips

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A large number of chemically unrelated drugs including cardiac glycosides, antihistaminics, antimalarials, local anesthetics, and various cations such as potassium and calcium have the ability of depressing various properties of heart muscle. This makes them useful in the treatment of certain disorders of heart rate and rhythm (Goth, 1964).

Recently, lidocaine, a local anesthetic, has been found to be effective in the treatment of cardiac arrhythmias (Weiss, 1960). The mechanism for the antiarrhythmic effect of lidocaine appears to be due to the depression of the heart similar to that produced by quinidine and procaine. When the heart is depressed, myocardial automaticity, the ability of heart cells to discharge spontaneously, is depressed; the time required for the conduction of impulses through the myocardium is prolonged; and the effective refractory period of the myocardium, that period during which

the heart muscle can not respond with a conducted beat after electrical stimulation, is also prolonged (Hoffman and Cranefield, 1960; Frieden, 1965). Quinidine and procaine amide also decrease mycardial contractility and blood pressure; while, in contrast, therapeutic doses of lidocaine do not (Frieden, 1965).

Cocaine, although it is a local anesthetic agent and possesses the same cardiac depressant actions as lidocaine, differs in that it also blocks or prevents the uptake of norepinephrine by the heart (Whitby et al., 1960; Muscholl, 1961; Iversen, 1963). Norepinephrine is the chemical mediator, stored in nerve terminals of the sympathetic division of the autonomic nervous system, which is released by impulses traveling down the sympathetic nerve (Goth, 1964). Since cocaine prevents the uptake of norepinephrine into nerve terminals, an important mechanism for inactivating norepinephrine (Trendelenburg, 1963), it enhances the actions of norepinephrine whether injected or released by nerve activity.

It has been suggested that cardiac glycosides exert at least part of their actions on the heart by releasing norepinephrine from its storage sites (Tanz, 1964; Levitt et al., 1966). This made it of interest to investigate the relationship between the release and uptake of norepinephrine and the arrhythmic action of ouabain with the effects of cocaine and lidocaine on the uptake of tritium-labelled ouabain.

METHODS

Guinea pigs of either sex ranging in weight from 200 to 400 g were sacrificed by cervical dislocation and their hearts immediately removed and placed in a modified Chenoweth-Koelle (C-K) solution (pH 7.35-7.4) continuously oxygenated with 95% O_2 - 5% CO_2 at 29 ± 1 C. Two right ventricle strips (30 to 70 mg) were impaled on bipolar platinum electrodes in the muscle holder. A Grass S5 stimulator was used to deliver square wave pulses of 5 msec duration, 2 pulses/sec, at suprathreshold voltage. The contractile force was recorded by a Grass Polygraph via a Grass FT-03 force-displacement transducer which was connected to the free end of the muscle. All strips were allowed to equilibrate for approximately 30 min. Then for a period of 15 min either cocaine, 10 μg/ml, or lidocaine, 10 μg/ml, was added to the bath followed by 0.12 μg/ml ^{3}H-ouabain for 20 min. After rinsing twice with fresh C-K solution, the muscle was homogenized and the homogenate centrifuged for 10 min. From an aliquot of the supernatant fluid, the amount of radioactivity for each sample was determined by a Packard Tri-Carb Liquid Scintillation Spectrometer, expressed as counts/min/mg.

Experiments to determine the influence of cocaine and lidocaine on ouabain-induced arrhythmias were conducted in a similar manner, although in this case the strips were exposed to cocaine and lidocaine for a period of 20 min and tritium-labelled ouabain was not used.

Standard statistical methods were used to analyze the data. All values were expressed as mean ± standard error. The Student's *t* test was employed to determine significance between groups of data. A *P* value of 0.05 was considered to be statistically significant (Snedecor, 1956).

RESULTS

Induction of arrhythmias by ouabain—The effects of cocaine and lidocaine on the induction of arrhythmias by the cardiac glycoside, ouabain, were determined. The end point established was either the development of spontaneous, automatic contractions or the failure of the ventricle strip to respond to every electrical impulse.

The response of the ventricle strips to a single concentration of

ouabain (1.5 μg/ml) was determined. This concentration was chosen since it will induce arrhythmias within approximately 15 min in control preparations.

Cocaine did not significantly affect the time required for the induction of arrhythmias by ouabain. Arrhythmias in cocaine-treated strips occurred within 15.0 ± 3.3 min, compared with 12.5 ± 5.7 min in control strips. However, strips which were pretreated with lidocaine required a significantly greater period of time for arrhythmias to develop, 28.9 ± 4.7 min as compared with 12.5 ± 5.7 min for controls.

Contractile effects of ouabain—The most important and useful therapeutic action of a cardiac glycoside, such as ouabain, is the increase in the force of contraction which it produces in the heart.

The initial contractile forces of the three groups of ventricle strips were comparable. When the strips were given cocaine, 10 μg/ml, before adding ouabain, cocaine significantly increased myocardial contractile force. The subsequent addition of ouabain (0.12 μg/ml) did not further increase the force of contraction. In contrast, pretreatment of the strips with lidocaine, 10 μg/ml, had no significant effect on the force of contraction until ouabain was added. The maximum force of contractions developed in all three groups, in the presence of ouabain, did not differ significantly.

Uptake of ^{3}H-ouabain—After 20 min exposure to ^{3}H-ouabain, 0.12 μg/ml and 0.15 μc/ml radioactivity, control ventricle strips contained 38 ± 2 cpm/mg radioactivity. In ventricle strips pretreated with 10 μg/ml of either cocaine or lidocaine, the amount of radioactivity present in the tissue after 20 min exposure to ^{3}H-ouabain was significantly reduced. Cocaine-treated strips contained 27 ± 2 cpm/mg, of radioactivity and lidocaine-treated strips, 22 ± 1 cpm/mg, as compared with 38 ± 2 cpm/mg for controls.

Discussion

Both cocaine and lidocaine exert comparable direct antiarrhythmic, depressant effects on heart muscle (Hoffman and Cranefield, 1960; Frieden, 1965). This made of interest the finding that pretreatment of ventricle strips with lidocaine delayed the onset of arrhythmias induced by ouabain while pretreatment with cocaine did not. The release of autonomic mediators (including norepinephrine) in cardiac muscle by suprathreshold electrically driven stimuli has been observed by several investigators (Whalen, 1958; Vincenzi and West, 1963). This effect, called electrorelease, is thought to occur as a result of the passage of current sufficient to release norepinephrine from nervous tissue found within the myocardium. Cocaine can enhance the actions of norepinephrine by preventing its uptake into the tissue while lidocaine cannot. Thus, electrorelease could explain the difference in the actions of cocaine and lidocaine to delay the onset of ouabain-induced arrhythmias by the blockade of norepinephrine uptake by cocaine. Interference with norepinephrine-uptake mechanisms by cocaine would make higher concentrations of norepinephrine available to react with the heart muscle. Among the most prominent actions of norepinephrine on heart muscle are its ability to increase the automaticity of the muscle and to markedly increase contractile force. Thus, in the cocaine-pretreated strips, the electrorelease of norepinephrine from the muscle and the enhancement of its action by cocaine would indirectly cause effects which were additive with those of ouabain, since both ouabain and norepinephrine can increase automaticity. The indirect action of cocaine to increase automaticity due to the electrorelease phenomenon, would tend to cancel out the direct, cardiac-depressant action of cocaine to decrease automaticity and delay the onset of arrhythmias.

A similar interpretation can account for the differences in the effects of cocaine and lidocaine on the force of myocardial contraction after pretreatment and the subsequent responses attained with ouabain. In cocaine-treated strips, the force of contraction was significantly increased by norepinephrine released by suprathreshold driving stimuli, since cocaine prevented the normal inactivating mechanism of norepinephrine reuptake. Lidocaine, however, has no blocking action on the uptake of norepinephrine and did not alter the equilibrium established during the control period as a result of the electrorelease and reuptake of norepinephrine. Although the subsequent administration of ouabain increased significantly the contractile force in lidocaine-treated strips, ouabain failed to further increase the contractile force of cocaine-treated strips, since the force had already reached a maximum after cocaine.

The results of this study demonstrate that the uptake of ^{3}H-ouabain by isolated guinea pig ventricle strips can be reduced significantly by pretreatment of the ventricle strips with either cocaine or lidocaine. A reduction in the amount of ^{3}H-ouabain accumulated in ventricle strips per unit time could clearly explain the antiarrhythmic action exerted by lidocaine in this study. Although cocaine also significantly reduced the accumulation of ouabain in ventricle strips, the direct antiarrhythmic action of cocaine was cancelled out by the indirect effects of cocaine to enhance the actions of norepinephrine resulting from electrorelease.

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