Cardiac Rhythm I

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DEVELOPMENT OF AUTONOMIC NEUROEFFECTOR TRANSMISSION TO PACEMAKER CELLS OF THE EMBRYONIC HEART. K. Löffelholz* and A. Pappano. Department of Pharmacology, University of Connecticut Health Center, Farmington, CT 06032.

Intracellular membrane potentials were recorded from pacemaker cells in the sinus venosus of chick hearts from the fifth incubation day to the first week after hatching. Trains of impulses (1-100 Hz) were applied to the sinus venosus region of isolated atria bathed in Tyrode solution at 30°C. In hearts incubated for 11 days or more, stimulation for 2-5 sec caused cardioinhibition that was accompanied by membrane hyperpolarization and reduced action potential duration. These effects were blocked by atropine (10^{-7}g/ml) and by TTX (10^{-8} g/ml), but not by hexamethonium (10^{-5}g/ml). These data indicated that acetylcholine was released from intracardiac postganglionic cholinergic axons by propagated action potentials. Stimulation for 2-5 sec evoked cardioacceleration after hatching (21 days). The acceleration was associated with an increased rate of slow diastolic depolarization and was blocked by propranolol (10^{-6}g/ml). Previous studies have shown that postjunctional cholinergic and adrenergic receptors are present by the third incubation day. It is concluded that during ontogenesis of the chick heart: 1) the postjunctional receptors for the neurotransmitters are operative before the appearance of autonomic neuroeffector transmission, and 2) adrenergic transmission develops later than does cholinergic transmission. (Supported by USPHS Grant No. HL-13339.)

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DIFFERENCES IN EFFECTS OF ANTIARRHYTHMIC AGENTS ON CELL CULTURES. R. J. Ertel, G. Ouyang‡ P. Gifford‡ F. R. Franke* and D. E. Clarke. Univ. of Pittsburgh. Sch. of Pharmacy and The Western Pennsylvania Hosp., Pittsburgh, Pa. 15213

Various concentrations of quinidine (Q), procainamide (PA), diphenylhydantoin (D), lidocaine (L), propranolol (P) and bretylium (B) were studied on cultured myocardial cells obtained from 7-day old chick embryos. The effects obtained on the spontaneous beating rate (SBR) and number of beating cells (NBC) in cultures derived from whole hearts are shown.

	SBR	NBC	
Q,PA	++	↔	+ = increase
D,L	+	+	- = decrease
B,P	↔	+	↔ = no change

Q and PA changed the monolayer of synchronously beating cells into two distinct cell populations, one showing an enhanced rate whereas the other exhibited a decreased rate. This phenomenon was absent in cell cultures derived solely from ventricular cells, whereas the effects of the other antiarrhythmics were not qualitatively altered. Surprisingly, B exhibited an anti-adrenergic action which appears to occur at the level of the β-adrenotropic receptor. The experimental observations provide a classification of the antiarrhythmic agents which is closely allied to that based on electro-physiological data and clinical usage in man. This close correlation suggests that responses of chick myocardial cell cultures are highly representative of adult mammalian myocardial mechanisms. (Supported by NIH Grant No. HL-14823).

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METHYLCHLOROFORM-INDUCED FIBRILLATION IN THE MOUSE. A.M. Strosberg‡ L.G. Johnson* and L.M. Miller* (Spon: R.K. Richards). Dept. of Pharmacology, Inst. of Clin. Med., Syntex Research, Palo Alto, Cal. 94304

Methylchloroform-induced fibrillation in the mouse has been employed as a screening procedure for the evaluation of antiarrhythmic properties of compounds (Hermansen, Acta pharmacol. et toxicol. 28: 17, 1970). We have attempted to clarify the mechanism of this fibrillation. Adrenalectomized mice and mice pretreated with 10 mg/kg of P-286 (a compound which blocks the release of adrenal catecholamines) were not protected against methylchloroform-induced fibrillation. Mice pretreated with reserpine (5mg/kg) and reserpine pretreated adrenalectomized mice were protected. The greatest protection was observed following intraperitoneal pretreatment with β-blockers (e.g. propranolol, 3mg/kg). Commonly used antiarrhythmic drugs protected only at enormous and near toxic dose levels (e.g. lidocaine, 50mg/kg and quinidine, 50mg/kg). Our results suggest that methylchloroform-induced fibrillation in the mouse cannot serve as a test for compounds effective against non-adrenergic mediated arrhythmias. However, it does appear to be a rapid and inexpensive screening procedure for detecting cardiac β-receptor blocking activity.

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TIME COURSE OF SUSCEPTIBILITY TO EPINEPHRINE-INDUCED TACHYARRHYTHMIAS IN THE CAT FOLLOWING INHALATION OF AEROSOL PROPELLANT. Emanuel B. Thompson* and Willard S. Harris*. Univ. of Illinois Med. Ctr., Chicago, Illinois 60612 (Spon: T. C. West).

Inhalation of high concentrations of aerosol propellants, e.g., CCl_2F_2, is known to cause sudden death in man, sometimes minutes after the end of exposure, and to sensitize dogs to severe epinephrine (Epi)-induced ventricular tachyarrhythmias. To assess the duration and disappearance rate of myocardial sensitization, we injected 13 pentobarbital-anesthetized cats i.v. with 4 or 8 μg/kg Epi before a 4 min inhalation of 37% CCl_2F_2 -21% O_2 -42% N_2 and periodically for 10 min after the end of the inhalation. Electrocardiograms and intraarterial pressures were recorded, and arterial blood levels of CCl_2F_2 were measured by gas chromatography. Before exposure to CCl_2F_2, no cats had Epi-induced ventricular tachyarrhythmias; after CCl_2F_2, all developed Epi-induced ventricular tachyarrhythmias. With 8 μg/kg Epi, 8 of 8, 7 of 8, 2 of 7, and 1 of 4 cats had Epi-induced ventricular tachyarrhythmias at 3, 5, 8 and 10 min post CCl_2F_2 respectively. In summary, susceptibility to Epi-induced ventricular tachyarrhythmias persisted after the end of CCl_2F_2 exposure, varied inversely with time as did the CCl_2F_2 blood levels, and sometimes lasted as long as 10 min postinhalation of CCl_2F_2.

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ACUTE AND CHRONIC ADMINISTRATION OF MORPHINE SO_4 EFFECT ON HEART RATE AND VENTRICULAR CONTRACTILE FORCE. A. E. Lucas*, J. Hinkebein*, R. Kimbler* and T. D. Darby. Department of Pharmacology, University of Louisville Health Sciences Center, Louisville, Kentucky 40201.

The studies were carried out in anesthetized mongrel dogs. Ventricular contractile force (IST) was measured by the strain gauge arch technique (P.S.E.B.M. 84:263, 1953). Arterial blood pressure (BP) was obtained from the femoral artery. Heart rate was determined from these recordings. Alterations in the cardiovascular status were produced by administration of cardiovascular drugs: Methoxamine and Nitroglycerin. The response to norepinephrine was obtained. After these control procedures the animals were challenged with 10 mg/kg of morphine SO_4 IV. The alterations in cardiovascular status were repeated. Vagotomy was completed and the procedure repeated. These same studies were carried out in dogs which were treated with increasing doses of morphine for 28 days. It was found morphine stimulates the parasympathetic reflex control (PRC) of heart rate in the acute studies, while in the chronic animals the PRC was markedly depressed, suggesting sympathetic predominance. Pretreatment with reserpine for 3 days or concomitant administration of morphine and reserpine for the last 14 days of the 28-day morphine treatment enhanced the PRC in the acute animals and abolished the PRC depression in the chronic animals. (Supported by Kentucky, Louisville and Jefferson County Heart Association Grant #64315.)

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THE EFFECTS OF ISOPROTERENOL ON CARDIAC CONDUCTION IN MAN Rajesh Dhingra*, Edward Winslow*, Shahbudin Rahimtoola*, Maurice Pouget*, and Kenneth Rosen* (SPON: Lawrence Isaac). Univ. of Illinois Hospitals, Chicago, IL 60612

His bundle (H) recordings were obtained in 43 patients (pts) during isoproterenol (Isp) infusion. The group consisted of 5 with normal and 38 with conduction disturbances. The mean ± SEM A-H interval in 30 pts with normal A-H (<130 msec) was 98 ± 3.1 msec prior to and 77 ± 3.1 msec during Isp. Mean A-H in 9 pts with prolonged A-H was 192 ± 17.1 msec prior to and 146 ± 14.6 msec during Isp. The mean H-V in 29 pts with normal H-V (<55) was 46 ± 1.0 msec prior to and 41 ± 1.0 msec during infusion. In 11 pts with prolonged H-V, the mean values were 68 ± 2.7 msec prior to and 59 ± 2.7 msec during Isp. All these decreases were significant ($p<.01$). The following improvements in conduction were noted in pts with 2° and 3° A-V blocks during Isp: 1) total reversal of 2° block proximal to H in 2 of 3 pts, and in 1 of 2 pts with block distal to H, 2) development of 2:1 conduction in 1 of 3 pts with 3° A-V block and 'split' H potentials, and 3) development of 3:1 conduction in 1 of 3 pts with 3° A-V block distal to H. In summary, pharmacological actions of Isp include facilitation of both normal and depressed conduction in the A-V node and the His Purkinje system.