CARDIOVASCULAR PHARMACOLOGY[1]

By Theodore C. West and Noboru Toda
Department of Pharmacology, University of Washington School of Medicine, Seattle, Washington

The limited space allotted to this review has restricted the emphasis to research reports appearing in the English language literature during the period April 1965 through May 1966, with few exceptions. In general, the publications reviewed are those of greatest interest to the reviewers. However, it is hoped that both the scope of the review and the items included will represent the type of research in cardiovascular pharmacology carried on throughout the world during the period covered.

The review is divided into two main sections, cardiac and vascular, with the bulk of the material contained in the first category. Within the cardiac group, the main subheadings include drugs affecting autonomic function in the heart, nonautonomic cardiotonic agents, and drugs affecting rhythmicity. By far the greatest emphasis in cardiovascular pharmacologic research during the past year is found in the realm of the adrenergic neurotransmitter and its role in drug action, accounting for the extreme emphasis assigned in this review to adrenergic mechanisms.

DRUGS AFFECTING CARDIAC FUNCTION

Because drugs modify existing physiologic processes, it is anticipated that pharmacologic effects will result from the actions of chemical agents on the electrical and mechanical properties of cardiac tissue, acting either directly on these properties, or indirectly through the mediation of intracardiac transmitters. However, it does not appear helpful to organize the review according to drug effects on physiologic properties of the heart. Consequently, in the empirical organization which is used, the action of drugs on physiologic mechanisms will be described when possible and when appropriate.

Autonomic Function

Drug effects on cholinergic transmitter function.—Pharmacologic and physiologic evidence continues to accumulate relative to the content and function of acetylcholine (ACh) in cardiac tissue. An electron microscopic study of canine atria and ventricles in normal and totally denervated hearts illustrated the persistence of neural structures after denervation (87). The structures were presumed to be postganglionic, possibly cholinergic. If so, histologic evidence for the cholinergic innervation of ventricular as well as atrial myocardium was presented.

[1] The following abbreviations will be used: ACh (acetylcholine); HC-3 (hemicholinium No. 3); DMPP (dimethylphenyl-piperazine); NE (norepinephrine); DCI (dichoroisoproterenol).

Several studies have illustrated the pharmacologic implications of the release of neurotransmitters by the local electrical stimulation of the myocardium. In the anesthetized dog, postdrive slowing was potentiated by physostigmine and depressed, but not abolished, by atropine (65). The resistance of postdrive bradycardia to atropine was presumed to be indicative of a cellular potassium shift in addition to the cholinergic mechanism. Field stimulation during the myocardial refractory period in guinea pig atria and in atria and papillary muscle from kittens, revealed a cholinergic component sensitive to block by atropine (15). A graded release of ACh was achieved in direct proportion to the frequency of electrical stimulation. The negative chronotropic response to local nerve stimulation by a punctate electrode on the S-A node was shown to vary as a direct function of the concentration of Ca (120). The sensitivity to exogenous ACh was altered only at the extremes of Ca concentration (0.11 and 11.0 m*M*), leading to the interpretation that the release of ACh from postganglionic stimulation was in direct relation to the Ca concentration.

Acetylcholine was shown to be bound largely in the nuclear fraction of rabbit and rat heart, but in the rat heart ACh is also concentrated in the microsomes (77). Hemicholinium No. 3 (HC-3) reduced the content of ACh in the nuclear, but not in the microsomal fractions, and diminished the nuclear fraction to about the same extent in vagally stimulated and nonstimulated atria. However, HC-3 reduced ACh in the electrically stimulated, but not in nonstimulated cat atria (53). Pretreatment with HC-3 also prevented the increased concentration of ACh which normally results from stimulation.

The cholinergic effects of local nerve stimulation in rabbit atrium were blocked by HC-3 in the presence of repetitive nerve stimulation, although the adrenergic effects were not altered in either nontreated or atropine-treated preparations (119). These results were interpreted to indicate that a cholinergic link is not essential to adrenergic excitation in the heart. In cat atria subjected to transmural electrical stimulation, HC-3 blocked the negative chronotropic effects of low frequency (1 and 2 cps) but not of high frequency (4 and 5 cps) stimulation (125). The separation of the frequency effects might have been related to the spread of current at the higher frequencies, or to the lack of insufficient time for maximal block by HC-3.

In the rat atrial-vagus preparation, the negative chronotropic and inotropic effects of nicotine and dimethylphenyl-piperazine (DMPP) were sensitive to HC-3 combined with vagal stimulation, as well as to nicotine, atropine, bretylium, and hexamethonium (26). Hemicholinium blocked the positive effects of nicotine, but not those of DMPP, whereas chronic pretreatment with reserpine failed to reduce the positive effects of nicotine but blocked those of DMPP, suggesting pharmacologically distinct actions of nicotine and DMPP. Because toad ventricular contracture did not develop in response to 120 m*M* K in Ca-free solutions, but 2 m*M* nicotine caused prompt contracture in such solutions without altering the resting membrane potential, it was concluded that nicotine acts distally to the membrane elec-

rical event, but proximally to the contractile system, possibly by the mobilization of bound cellular or membranal Ca (89).

The local, intracoronary arterial administration of ACh and other autonomic drugs exerted local changes in the myocardial contractile force in the area supplied by the injected vessel (57). Acetylcholine applied by this method antagonized the positive inotropic response to norepinephrine (NE) or to stellate ganglion stimulation, and caused a positive inotropic "rebound" upon cessation of the infusion or the stimulation. The effects of ACh were blocked by atropine but not by hexamethonium, pronethalol, bretylium, or pretreatment with reserpine. It was concluded that ACh releases an active substance in the heart which apparently is not NE. The method represents an intriguing approach utilizing isolated tissue concepts *in situ*.

Reserpine applied *in vitro* at 10^{-5} g/ml caused arrest of the spontaneous beat in guinea pig atrium within approximately two hours (113). An early augmentation of the negative chronotropic response to vagal stimulation was followed by inhibition. Although the action was thought to resemble an uncoupling of oxidative phosphorylation, a direct action of reserpine on neural excitability was not ruled out.

Drug effects on the adrenergic neurotransmitter.—In the totally denervated transplanted dog heart, the myocardial content of adrenergic nerves was concluded to govern the extent to which the heart will bind and store DOPAmine and NE, and synthesize NE (95). In the denervated heart, the content of NE was 1.2 per cent of normal, whereas the binding and storage was 6.1 per cent of normal. The activity of catechol oxymethyl transferase (COMT) and monoamine oxidase (MAO) were little changed in the denervated heart. The cardiac NE content of immunosympathcctomized rats was 5 per cent of normal and the H^3-NE uptake was reduced to 10 per cent of normal, although the activity of COMT and MAO in the immunosympathectomized mouse heart was not altered (59). The ventricles and atria of immunosympathectomized rats were depleted of NE, but although atrial DOPA decarboxylase decreased, that in ventricles did not (63). The content of endogenous NE in isolated atria of cats was maximal when the stimulation frequency of the attached cardioaccelerator nerve was from 1 to 4 cps (41). Histologic examination indicated a greater number and intensity of nerve fibers in the stimulated tissues and it was concluded that rebinding of NE occurs at maximal efficiency at low frequencies of stimulation.

In guinea pig atria, and in kitten atria and papillary muscle, the maximal adrenergic response to field stimulation was identical to that induced by NE (15). The response was enhanced by cocaine, reduced by β-adrenergic blockers and by chronic pretreatment with reserpine, and abolished by chronic denervation. Norepinephrine was shown not to play a role in the interval-strength relationship in myocardium, provided that suprathreshold strengths of stimulation were not used (64). A significant modification of the interval-strength curve was shown with reserpine (chronic pretreatment) and propranolol, but only with doses in excess of those necessary for deple-

tion or block of catecholamines. Although epinephrine was the predominant catecholamine in frog heart, DOPAmine was most concentrated in the sinus venosus of this species (5), as well as in the S-A node of the dog (2).

The uptake of NE in hearts of guinea pigs was not affected by repeated administration of α-methyltyrosine, which reduced cardiac catecholamines to undetectable levels (106). Only with tyrosine was the maximal rate of synthesis of NE achieved in isolated guinea pig hearts, permitting the conclusion that conversion of tyrosine to DOPA is rate-limiting in the synthesis of NE (74).

Electroaugmentation of ventricular performance (by paired-pulse stimulation) in the dog was not modified by pretreatment with reserpine or by pronethalol, and thus is presumed to be independent of stored adrenergic neurotransmitter (99).

It was shown in a small number of animals that the concentration of catecholamines in atria is higher than that in the ventricles in the rabbit heart, and that the restoration of catecholamines to control levels after a single dose of reserpine occurs most rapidly in atrial tissue (50). The rate of uptake of H^3-NE in isolated, perfused rat heart was not affected by pretreatment with reserpine, but the retention of H^3-NE in both the perfused and the *in situ* heart was depressed, presumably because of a rapid metabolism by MAO in the axoplasm (58). It was suggested that reserpine impairs the entry of NE into nerve storage granules and thereby exposes it to oxidation by MAO.

C^{14} α-methylnorepinephrine from α-methylDOPA displaced myocardial NE molecule for molecule, but the ED_{50} for reserpine to deplete radioactivity of the α-methylNE was about ten times that required to deplete the heart of norepinephrine (94). Hearts from guinea pigs pretreated with α-methyltyrosine 16 to 17 hours prior to sacrifice contained 63 per cent less NE than controls, but α-methylNE was demonstrated in the heart, suggesting that the depletion of NE was based on a displacement in addition to the inhibition of synthesis of NE (80).

In isolated atria of rabbits, reserpine applied *in vitro* at 10^{-5} g/ml depressed contractile force but had variable effects on the activity of cardiac phosphorylase (39). It was suggested that the effect on phosphorylase *a* resulted from the release of NE, but the experiments were not repeated in animals pretreated with reserpine. The ability of reserpine applied *in vitro* to deplete cardiac NE was studied in rabbit atria at different bath temperatures (38). At 23° C reserpine failed to reduce the content of NE, but a 40 per cent reduction of the transmitter was observed at 37°. In view of the observation that perfused hearts of rats and rabbits lose large amounts of NE as a result of anoxia (126), it is not clear whether the influence of temperature on reserpine applied *in vitro* results from a thermal effect per se, or from hypoxia. In the isolated, driven left atrium of the guinea pig at 37° C, the *in vitro* application of reserpine reduced the NE by 60 per cent within four hours and inhibited the uptake of norepinephrine (22). Bretylium, tyramine, cocaine, and

phenoxybenzamine also decreased the uptake of NE, but no correlation was found between the amount of NE depletion and the positive inotropic effect.

In isolated atria from chronically reserpinized rabbits and guinea pigs the response to tyramine, but not to nerve stimulation, could be restored by exposure to NE, suggesting that tyramine and nerve stimulation do not release NE from the same site (116). Reserpine pretreatment reduced the inotropic response of isolated guinea pig atria to field stimulation and to tyramine to about the same extent, but the chronotropic response to tyramine was more inhibited by pretreatment with reserpine than was the inotropic response, which was blocked to about the same extent as with field stimulation (15). Isolated papillary muscle from the left ventricle of human beings responded to tyramine by an increase in active tension in proportion to the content of NE, which ranged from 0.09 to 0.8 mg/g (27). In the guinea pig atrium, NE and α-methylNE were shown to be equally effective (103). Pretreatment with α-methylDOPA augmented the response to tyramine, *d*-amphetamine, and mephentermine, but not to adrenergic nerve stimulation, leading to the conclusion that indirectly acting amines and nerve stimulation affect NE at different storage sites.

In the rat heart, sustained concentrations of tyramine caused depletion of NE at a single exponential rate, but because tyramine is so rapidly metabolized, the concentration of tyramine was maintained in order to achieve a maximal rate of release (91).

The application of ACh to perfused guinea pig hearts mobilized cardiac norepinephrine, which was shown to increase in the perfusate (3). However, the content of tissue NE also increased, prompting the interpretation that the turnover of cardiac NE, associated with an increased synthesis, was augmented by acetylcholine. Although ACh plus Ca increases the release of catecholamines in organ perfusion experiments, no increase occurred when ACh was applied to isolated granules of rat adrenal medulla either alone or in combination with calcium (46). In rabbit atria, ACh increased the spontaneous rate and amplitude of contraction at higher Ca concentrations, although some depression was caused at lower concentrations of Ca (20). The positive response to nicotine was directly related to the Ca concentration, but the response to tyramine and to NE was almost unaffected by Ca. The data were interpreted to support the hypothesis of a cholinergic link in adrenergic excitation.

Guanethidine was shown to displace norepinephrine from rat heart in a ratio of three moles of guanethidine for each mole of NE (24). However, the correlation of these data with adrenergic blockade is difficult because the blocking action of guanethidine was defined in terms of ocular ptosis, whereas cardiac catecholamines were chemically determined.

Mercaptoethylguanidine (MEG) lowered the levels of cardiac NE in cats and mice by a mechanism independent of its ganglion blocking action (30). In isolated cat atria, MEG reduced the content of NE and induced a positive inotropic effect. In the rat heart, the maximal retention of several

sympathomimetic amines in the microsomal fraction was more dependent upon the catechol group than on the β-hydroxyl group (85). Amines lacking both catechol and β-hydroxyl moieties do not bind to microsomes.

Drug effects on adrenergic receptor systems: activation.—Cocaine augmented the cardiac inotropic effects of norepinephrine more than its vascular effects (45). Cocaine slightly reduced the response of cardiac output to tyramine, but greatly depressed the vascular effects of tyramine, whereas the response of stroke work to sympathetic nerve stimulation was increased after cocaine. Cocaine potentiated blood pressure responses to NE more than to epinephrine in the pithed rat, and decreased the uptake of cardiac H^3-norepinephrine more than that of H^3-epinephrine (118). Pretreatment by reserpine exerted similar effects, but they were presumed to have occurred by a different mechanism. In the dog, cocaine potentiated the response of myocardial contractile force more to norepinephrine than to epinephrine and failed to potentiate the response to isoproterenol (52). The effects of cocaine on the uptake of the respective H^3-catecholamines followed a similar pattern, providing direct evidence for the hypothesis that the potentiative effect of cocaine is based on a depression of uptake of catecholamines.

Norepinephrine was shown to accumulate in perfused heart by two processes, one occurring at low, the other at high concentrations of NE (19). The structural requirements of sympathomimetic amines capable of blocking the uptake of NE did not correlate with the known structure-activity relationships for either α- or β-receptors in the case of either uptake process.

In the anesthetized dog and the dog heart-lung preparation, desmethylimipramine (DMI) was shown to exert positive inotropic and chronotropic effects (61). The drug sensitized the cardiovascular system to NE but not to epinephrine or isoproterenol. Its sympathomimetic activity was blocked by dichloroisoproterenol (DCI), guanethidine, and pretreatment with reserpine. However, the response to stimulation of the stellate ganglion was diminished. It was concluded that DMI acts in the heart to release NE, and that it produces a specific supersensitivity to NE at its cardiac receptors. The differential effect on the response to norepinephrine and isoproterenol resembles the effect of cocaine (52).

Adrenergic receptors in the frog heart appeared to be predominantly β for both the chronotropic and inotropic actions of adrenergic amines, in terms of the relative potencies of norepinephrine, epinephrine, isoproterenol, and phenylephrine (34). It was postulated that the rat ventricle contains α- and β-stimulatory receptors and α-inhibitory receptors, in view of the interactions between several agonists and antagonists (124). However, the possibility that the adrenergic blockers might have exerted variable effects on the catecholamine uptake was not considered.

Over a range of pH from 6.5 to 9.5, the maximal response to epinephrine occurred at pH 7.5 in the turtle heart (51). The dose-response relationship of the epinephrine cation suggested that the active form of epinephrine is the

cation, but it was surmised that the sensitivity of the cardiac adrenergic receptor is pH sensitive. The increase in oxygen uptake produced by epinephrine in the isolated rat heart was independent of chronotropic or inotropic activity, because it occurred in hearts arrested by excess potassium (23). The rise in oxygen consumption was accompanied by a rise in glycerol release, but not by free fatty acids, suggesting that endogenous lipids are the source of the release of glycerol.

In human beings the cardiovascular response to isoproterenol resembled the effects of exercise (98). The increase in heart rate was not essential to the increased cardiac index, which was elevated by isoproterenol in patients in whom the heart rate was held constant by atrial pacing. Denervation of the S-A node of the dog caused supersensitivity of the node to norepinephrine, although functional sympathetic nerves existed in other parts of the heart (31). The effect was not matched by chronic, bilateral stellate ganglionectomy or by chronic pretreatment with reserpine.

Norepinephrine and methylnorepinephrine were equally effective as adrenergic agonists in hearts from reserpine pretreated, open-chest vagotomized dogs (29). DOPAmine and methyl-DOPAmine were also quantitatively similar, but methylDOPA was less effective than DOPA. Reversal of blockade to the response to stimulation of the right cardioaccelerator nerve followed the same pattern. The reversal by methylDOPA was prevented by NSD-1024, an inhibitor of DOPA decarboxylase, and quickly depressed that of DOPA, but it did not modify the reversal to NE or DOPAmine or their methylated derivatives.

In contrast to the positive dromotropic action of catecholamines in specialized cardiac tissues, neither norepinephrine nor epinephrine produced detectable effects on conduction velocity on driven isolated papillary muscle from the Rhesus monkey (6).

Drug effects on adrenergic receptor systems: blockade.—The compounds MJ-1999 and MJ-1998 were observed to act on isolated rabbit atria as potent and selective β-adrenergic blockers, with low chronic toxicity in the intact animal (78). MJ-1999 blocked the positive inotropic and vasodilator response to isoproterenol in anesthetized dogs and the coronary dilation associated with anoxia in the intact dog and in the dog heart-lung preparation (36). Blockade of the positive inotropic and positive chronotropic response to isoproterenol was as follows in the isolated cat heart: MJ-1999 = pronethalol > MJ-1998, whereas in the anesthetized dog MJ-1999 > pronethalol > MJ-1998 (107). Direct cardiac effects were not seen after MJ-1999, although pronethalol had slight stimulatory effects.

The N-isopropyl and N-butyl derivatives of *p*-nitrophenylethanolamine (INPEA and BNPEA) and N-isopropylmethoxamine (IMA) were compared with dichloroisoproterenol (84). Adrenergic blockade followed an order of potency of the series: DCI = pronethalol > INPEA > BNPEA > IMA.

Sinus arrhythmia in dogs anesthetized with morphine-chloralose was

resistant to blockade by propranolol in doses (0.5 mg/kg, intravenously) high enough to abolish the response to isoproterenol injected in doses of 2 to 9 mg/kg, intravenously (49). The investigators assumed that propranolol had produced complete adrenergic blockade to cardiac sympathetic nerve excitation and interpreted the results to indicate a nonadrenergic basis for sinus arrhythmia. The time course for both the agonistic and antagonistic effects of pronethalol revealed in the anesthetized dog an early (15 min) slight sympathomimetic effect after 2.5 mg/kg pronethalol, intravenously (28). Ventricular systolic pressure and oxygen consumption were increased, whereas arterial pressure and peripheral resistance fell, but after 30 minutes only the arterial pressure remained lower than control and the normal response to injected epinephrine was blocked. Whether the apparent sympathomimetic effects of pronethalol were direct, or a reflex response to the reduced arterial pressure, was not clear. In dogs anesthetized with pentobarbital, pronethalol administered at the rate of 1 mg/kg every five minutes produced a depression of heart rate, ventricular force, cardiac output, and arterial pressure at a total dose of 4 mg/kg, although 5 mg/kg was required to abolish the response to isoproterenol (122). The investigators concluded that the direct depressant effect of pronethalol occurred at lower doses than those required for adrenergic blockade. Dose-response curves for the response to isoproterenol of myocardial contractile force and peripheral resistance in the anesthetized dog were shifted to the right after propranolol as a function of the dose of the antagonist, but the maximum was not modified by propranolol, suggesting the existence of a classic competitive blockade (86). The cardiac output of patients with ischemic heart disease was diminished by 22 per cent following 2 mg of propranolol given intravenously, whether the patients were at rest or responding to exercise (48). The degree of depression of output induced by propranolol was greater than that of heart rate; the decrease in cardiac work was considered beneficial for patients with angina pectoris. In the anesthetized dog, the adrenergic effects of DCI (0.5 mg/kg) on blood pressure, myocardial contractile force, and heart rate were blocked by pronethalol in a dose which blocked 90 to 95 per cent of the cardiostimulatory effects of isoproterenol (123). The authors concluded that the sympathomimetic activity of DCI is more closely related to that of the β-hydroxyphenethylamines than to the catecholamines. The positive inotropic response to DCI in atria from rats pretreated with reserpine was abolished, although the chronotropic response was not (121). In normal atria, pretreatment with cocaine, bretylium, DCI, pronethalol, guanethidine, and isoproterenol either reduced, abolished, or reversed the cardiostimulatory effects of DCI (121).

In guinea pig atria challenged by NE, tyramine, or butyrylcholine, pronethalol and propranolol competitively blocked NE responses but were said to block tyramine noncompetitively (11). As a blocker of β-receptors, propranolol was 17 times more potent than pronethalol.

Other effects on adrenergic function.—Although chronic administration of guanethidine reduced the basal heart rate in rats, it did not inhibit the increase in heart rate induced by chronic treatment with thyroxine (9). However, bretylium, which did not alter the heart rate in untreated rats, depressed the chronotropic response to thyroxine. The chronotropic and inotropic responses to epinephrine and to norepinephrine in isolated atrial and ventricular preparations in rats were not potentiated in hearts from animals pretreated with thyroxine (117). In the dog, thyroxine increased heart rate and increased phosphorylase *a* but did not potentiate the actions of catecholamines on those parameters (117). The investigators concluded that catecholamines are essential for thyroxine activity, but that thyroxine does not alter the sensitivity of the adrenergic receptors.

Both thyroxine and triiodothyronine increased heart rate, arterial pressure, and the activity of phosphorylase *a* in rats but did not potentiate the effects of epinephrine on the same parameters (56). Acetylcholine and pronethalol reversed, and pretreatment with reserpine prevented the stimulatory effects of thyroxine. The cardiovascular responses of hyperthyroid or hypothyroid dogs to exogenously applied or endogenously released catecholamines were not different from those of euthyroid animals (81). Although most of the studies involving thyroxine failed to illustrate sensitization to NE by thyroxine, isolated atria from rabbits pretreated with thyroxine were characterized by a higher spontaneous rate, increased NE content, and increased sensitivity to NE applied to the muscle bath (70). A correlation between spontaneous rate and NE content was shown. Any effects resulting from the application of thyroxine directly into the muscle bath were presumed to be caused by chelation of metal contaminants in the nutrient solution.

Severe hypothyroidism was produced in rats by a single intraperitoneal injection of I^{131} (12). Right ventricular strips from the resulting thyroid deficient animals were less resistant to ventricular stretch, but the frequency-force relationship and the effects of NE on force and the development of automaticity were not altered.

Cardiotonic Drugs—Glycosides

Eight naturally occurring glycosides of *Antiaris toxicaria* and three derivatives possessed digitalis-like activity, the greatest potency residing in the natural glycosides (25). In the isolated left atrium of the rabbit, ouabain exerted two opposing actions on the refractory period: (*a*) a release of NE which tended to decrease the refractory period, and (*b*) a direct action of ouabain tending to increase the refractory period (43). In the isolated, perfused cat heart, pretreatment with reserpine reduced the effectiveness of 5×10^{-7} g/ml ouabain, although the initial rate and force were not affected by reserpine (112). The contribution of reserpine-sensitive catecholamines to the action of ouabain was slight, but definite. However, it was reported that the

inotropic response to ouabain in driven left atria from reserpine-pretreated rabbits was not significantly different from controls (75). Reserpine did not alter the increase in oxygen consumption induced by ouabain nor did it prevent the onset of ouabain toxicity.

Chronic pretreatment by reserpine in dogs did not alter the effect of acetylstrophanthidin on net K influx in the heart (16). It did not modify the inotropic action of ouabain, but protected against the cardiac arrhythmias induced by ouabain by a mechanism only partly dependent on catecholamines. The response to ouabain by isolated papillary muscle from cats was significantly depressed by chronic pretreatment with reserpine or by exposure to dichloroisoproterenol, although neither of these impaired the inotropic response to excess Ca (111). Ouabain was able to restore automaticity to control atria arrested by the *in vitro* application of reserpine, but could not restart atria from chronically reserpinized hearts (109). The data were interpreted to illustrate the ability of ouabain to release stored catecholamines in heart.

Syneresis of cardiac myofibrils was inhibited by a relaxing factor (RF) from the same heart, but the action of RF was inhibited by the passage of electrical pulses through the reaction mixture (69). Although strophanthin-K did not affect RF per se, in concentrations of 10^{-6} and 5×10^{-7} g/ml, it potentiated the effect of electrical pulsing. It was also reported that electrical stimulation of suspensions of fragments of sarcoplasmic reticulum in cardiac and skeletal muscle caused the release of Ca taken up previously by the sarcoplasmic reticulum (68). Upon termination of electrical stimulation, re-uptake of Ca appeared in the sarcoplasmic reticulum fragments. The investigators considered the results to represent an *in vitro* demonstration of essential steps in excitation-contraction coupling. The relaxation induced by creatine phosphate in glycerinated cardiac fibers from dogs became progressively less as the preparation aged (33). Because ouabain (10^{-5} *M*) had no effect on either the contraction or relaxation of glycerinated fibers regardless of age, it was concluded that ouabain does not directly affect the relaxation system of the preparation.

Ouabain, 10^{-6} *M*, increased the availability of exchangeable Ca in isolated left atria from rabbits, both during the positive inotropic effect and later during the development of toxicity (44). Ouabain was calculated to have increased the uptake of Ca from 5.43 to 14.31 pmoles/cm^2 per beat. The authors assumed that ouabain affected calcium exchange, which then affected contractile force. Ouabain, 4.8×10^{-7} *M*, applied to driven rabbit papillary muscle, increased the intensity of the active state and increased the rate of contraction (32). These effects were similar to those occurring with increased frequency of contraction in the same preparation.

In the dog heart-lung preparation, the administration of 5×10^{-8} g/ml ouabain produced a prompt increase of K in the cardiac lymph (4 to 7.7 meq within 30 min), a K loss for which the heart was presumed to have been the the source (7).

Using an ATPase prepared from rabbit brain or from chicken kidney, it was shown that low concentrations of ouabain (10^{-11} to 10^{-8} M) caused stimulation of the Na-K-dependent ATPase in the presence of Na or K (93). At 10^{-7} M or greater, the enzyme was inhibited. The authors suggested two different receptor sites for ouabain on the same enzyme: one for stimulation and one for inhibition.

Only very high concentrations of ouabain were able to induce swelling, or to inhibit the deturgescence of cold-induced swelling in the cornea, although active transport of Na is thought to prevent corneal swelling normally (66).

It was shown in digitalized patients that digitalis intoxication often appeared upon conversion to sinus rhythm, although no indication of digitalis toxicity had been noticed prior to conversion (40). The authors recommended that digitalis be withheld for several days in patients for whom conversion was to be attempted.

In patients with complete heart block (with a fixed ventricular rate), cardiac glycosides were shown to exert a positive inotropic effect, thus indicating an increased stroke volume and cardiac output independent of ventricular frequency (10). The ability of ouabain to shorten the period of isometric contraction has thus been extended to the human myocardium functioning at a fixed ventricular rate.

In the closed chest anesthetized dog, paired-pulse stimulation prevented the onset of nodal or ventricular tachycardia during the intravenous infusion of ouabain, but did not increase the total dose at which ventricular fibrillation occurred (37). The fibrillatory dose was slightly decreased by paired-pulse stimulation. The difference between the control of localized ectopic beats and ventricular fibrillation might have been related to differential effects of ouabain on specialized and nonspecialized cardiac tissues.

In the isolated right atrium-vagus nerve preparation, ouabain in low concentrations (5×10^{-8} to 2×10^{-7} g/ml) augmented the chronotropic effects of vagal stimulation, but at 10^{-6} g/ml the negative chronotropic response to vagal stimulation was abolished, although cholinergic effects still occurred in the single cells of the S-A node and the sensitivity to exogenous ACh was increased (114). It was apparent that toxic concentrations of ouabain shifted the dominant pacemaker to a poorly innervated site.

Cardiotonic Drugs—Nonglycoside

In the trained, unanesthetized dog, 3′,5′-AMP mimicked the effect of catecholamines (73). Heart rate increased, arterial pressure fell, hyperglycemia occurred, and the free fatty acids diminished. Although DCI blocked the cardiovascular effects it did not alter the metabolic effects. None of the responses were blocked by propranolol or modified by theophylline or imidazole. Adenosine, AMP, ADP, and ATP produced quantitatively identical decreases in heart rate, myocardial tension, and arterial pressure in the anesthetized dog, leading to the interpretation that the cardiovascular action was dependent upon the adenosine moiety, not high energy phosphate bonds

(4). Several adenine derivatives (ATP, ADP, A-5-MP, adenosine, A-2-MP, and A-3-MP) caused bradycardia upon direct perfusion of the canine sinus node (60). Atropine did not modify the response and it was concluded that the D-ribose and amino groups, but not high energy phosphate bonds, were essential to the chronotropic activity of these compounds. In general, it appeared that adenine compounds exert cardiovascular effect independently of the high energy phosphate bonds, but whether the effects were related to the chelation of Ca or other ions (35) apparently was not considered.

Synthetic bradykinin produced in rats an increase in cardiac output, and a simultaneous decrease in arterial pressure and peripheral resistance (110). The intensity of these effects was dose-related. The skin fraction of total blood flow decreased, but whether it was a direct or indirect effect of the drug was not discussed.

Of a series of steroids compared with aldosterone for antagonistic action to ouabain in the cat papillary muscle, 2α-methyl 9α-fluorocortisol and deoxycorticosterone were relatively effective (71). The positive inotropic action of aldosterone was augmented at low (0.63 mM) concentration of Ca. The results prompted the suggestion that aldosterone can occupy two receptors, one for the contractile system and one related to cation transport, located in the cell membrane and important to ouabain-induced arrhythmias.

Positive inotropic responses in papillary muscle from monkeys were induced by a wide range of concentrations of aldosterone, although high concentrations caused a negative inotropic response (88). The effects of aldosterone were not altered by pronethalol.

A histone-like substance which inhibits the Mg-dependent microsomal ATPase system and potentiates ouabain inhibition of the enzyme was isolated from the nuclear fraction of heart muscle and other tissues (101). The same laboratory showed that histones isolated from cardiac muscle inhibit myocardial contractility and syneresis of actomyosin or myofibrillar suspensions (102).

The cardiotonic protein system termed cardioglobulin was extracted from mammalian plasma and tested on the frog heart for its inotropic properties and its effect on the uptake of Ca^{45} (47). It was believed that cardioglobulin, through several steps, released protein-bound Ca onto the myocardial cell.

The properties of a cardiotonic substance from mammalian plasma were tested in a variety of cardiac preparations both amphibian and mammalian, isolated and intact (90). In all species, the cardiotonic substance produced a positive inotropic effect that was not mediated by adrenergic neurotransmitters.

Drug Effects on Rhythmicity

Pronethalol and N-isopropyl derivative of p-nitrophenylethanolamine (INPEA) antagonized arrhythmias induced in the dog by sympathomimetic

amines, but only pronethalol suppressed ouabain-induced arrhythmias by an apparent nonspecific, quinidine-like action (105). β-Adrenergic blockade by pronethalol was not the mechanism by which this compound prevented arrhythmias induced by digitalis or the combination of hydrocarbons and epinephrine in the dog (79). By a mechanism involving specific adrenergic blockade, MJ-1999 antagonized arrhythmias produced in the dog by epinephrine and methylchloroform, but the drug was unable to suppress ventricular arrhythmias induced by ouabain or by coronary ligation (104). Pronethalol and propranolol both depressed the contractile force of driven left atria of rabbits, although MJ-1999 was not depressant in concentrations as high as 6.5×10^{-4} M (76). Cardiac depression was not associated with the blockade of β-receptors. The ability of pronethalol to reverse arrhythmias induced in the dog by acetylstrophanthidin was interpreted to reside mainly in a quinidine-like action, rather than from a β-adrenergic blocking action (8).

In the isolated, perfused heart of the cat, the direct ligation of the bundle of His resulted in a preparation with independent atrial and ventricular pacemakers (92). The administration of quinidine, either as a single injection or by perfusion, to this preparation reduced the atrial rate relatively more than the ventricular rate; the sensitivity of the atrial pacemaker was greater than that of the ventricular pacemaker (92). The activity of Na-K-activated ATPase from the cell membrane-microsomal fraction of toad cardiac muscle was depressed by quinidine (10 to 50 μg/ml) in direct proportion to the concentration (62). Tetraethylammonium, norepinephrine, epinephrine, or diphenylhydantoin did not influence the enzymatic activity.

Because a combination of insulin, glucose, and acetylcholine produces in the dog an atrial fibrillation believed by Leveque (72) to be related to the release of catecholamines, bretylium was administered. Bretylium induced a dose-dependent antifibrillatory action, but it was interpreted to be independent of its antiadrenergic action.

Emetine depressed conduction velocity and prolonged the refractory period in direct relation to concentration in isolated atria from rabbits (54). It was interpreted to be closely comparable in action to quinidine. Further study on rabbit atria, cat papillary muscle, and Purkinje fibers from sheep showed emetine to reduce the rate of depolarization and repolarization, to reduce the amplitude of the cardiac action potential, and to depress spontaneous activity in Purkinje fibers (55).

The central intraventricular injection of pentylenetetrazol, picrotoxin, and deslanoside in conscious dogs induced prompt ventricular tachycardia, convulsive seizure patterns, and hypertension (14). Hexamethonium and TEA blocked the cardiac arrhythmia but not the convulsive or pressor effects, with the conclusion that the arrhythmia was mediated by the efferent autonomic system.

The perfusion of aconitine (0.8 to 1.5×10^{6} g/ml) in isolated right atrial preparations from the rabbit induced a sustained atrial fibrillation (42).

Acetylcholine appeared to improve the arrhythmia, probably by synchronizing it, whereas epinephrine or atropine had the opposite effect.

DRUGS AFFECTING VASCULAR FUNCTION

In the isolated rabbit pulmonary artery, ACh, histamine, and serotonin all caused contracture and all caused about the same degree of depolarization (108). The results were interpreted to illustrate the unique nature of the vasoconstrictor action of norepinephrine.

The contracture produced by ouabain in isolated aortic strips was Ca-dependent and associated with an increase in Ca^{45} uptake, no change in Ca content, and thus an increase in the exchange of Ca (17). It was concluded that the action of ouabain on vascular smooth muscle may be mediated via a Ca mechanism in a manner similar to that shown for the heart from results which indicated that rabbit aortic strips are relatively resistent to ouabain *in vitro*, but develop an increased sensitivity to ouabain when placed in Ca-free solutions for short periods (18).

In the perfused rabbit ear preparation, the response to angiotensin did not appear to depend on the release of catecholamines, although it was considered that angiotensin may sensitize NE receptors and that angiotensin may enhance the catecholamine-releasing action of tyramine (100). In the isolated rabbit ear and in aortic strips, potentiation by guanethidine of the response to NE was dissociated from the inhibition of uptake of NE (82).

The supersensitivity to NE induced by cocaine, guanethidine, and methyl phenidate in the rabbit aortic strip may not be dependent upon the degree of binding of NE, because about 30 per cent of inhibition of binding can occur without alteration of the response to NE (83). Isolated femoral arterial preparations from dogs were shown to exhibit supersensitivity to single injections of NE in preparations from animals pretreated with reserpine (21). When a series of sympathomimetic amines was applied to helical strips of rabbit thoracic aorta, pulmonary and anterior mesenteric arteries, and inferior vena cava, the slope of the resulting dose-response curves was independent of structural alterations of the amines (13). In the peripheral microvasculature of the rat mesocecum, the administration of DCI increased the vascular reactivity to locally applied vasoconstrictor catecholamines while blocking the local vasodilator actions of isoproterenol (1). These results suggest the presence of β-adrenergic receptors in the rat mesenteric microcirculation.

The injection of ACh into the perfused accessory cephalic vein of the dog produced a venoconstriction apparently mediated through the release of catecholamines from extraneural stores (96). It was postulated for the vasculature of the dog hind limb that a cholinergic vasodilator mechanism and an adrenergic vasoconstrictor mechanism coexist in the same sympathetic nerve; that the adrenergic effect is not subserved by a cholinergic mechanism

(67). In rats and dogs the repletion of NE following pretreatment with reserpine varies in the different species, is dependent upon the dose of reserpine, and is not restricted to natural catechol derivatives but can actively result from false transmitters (115). It was of interest that the methylated catechols were able to restore activity more effectively at the higher doses of reserpine. Epinephrine was thought to exert vasodilation by a neural mechanism because it did not increase hind limb blood flow in denervated, pressure-stabilized animals (97).

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