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The effect of certain β-adrenoceptor antagonists on overdrive suppression

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Summary

1. Propranolol, as the racemate and the (+)- and (−)-isomers (400 μg/l.) and practolol (50 mg/l.) were tested for their effects on atrial and ventricular rates and on the duration of overdrive suppression (ODI) in isolated perfused cat hearts with surgically-induced heart block.

2. Racemic propranolol and the (+)- and (−)-isomers prolonged ODI and slowed the rate of the ventricular pacemaker; the (+)- and (−)-isomers also reduced the rate of the atrial pacemaker. Practolol shortened ODI and increased the rate of the atrial and ventricular pacemakers.

3. The (+)- and (−)-isomers were more potent than the racemate; the (−)-isomer was more potent than the (+)-isomer. The results suggest there is a stereospecific mechanism involved in the biological distribution of propranolol.

4. Twenty-four hours after reserpine treatment (5 mg/kg, i.p.) practolol continued to increase the rate of the atrial and ventricular pacemakers but did not shorten ODI.

5. The mechanism by which these agents affect myocardial excitability and automaticity is discussed.

Introduction

It is now generally recognized that the sinus node is the pacemaker of the heart not only because it discharges latent pacemakers before they can attain their threshold to discharge but also because it inhibits them as a result of its faster rate. Thus, when a potential pacemaker is driven at a rate higher than its intrinsic rate, the cessation of stimulation is followed by a period of quiescence (overdrive suppression). Although overdrive suppression was originally described by Gaskell (1883) (Gaskell's rhythm of development), it has only been relatively recently that studies of the mechanisms involved in this phenomenon have been conducted (West, 1961; Lange, 1965; Lu, Lange & Brooks, 1965; Alanis & Benitez, 1967; and Vassalle, Vagnini, Gourin & Stuckey, 1967). It has been proposed that in the atrium the process involves the liberation of acetylcholine while in the ventricles it involves loading the Purkinje fibres with sodium so that the amount is approximately double that normally present in spontaneously discharging Purkinje fibres (Vassalle, 1970).

It occurred to us that since the action of drugs on pacemaker activity had largely been determined by studying their effects on spontaneously discharging pacemakers, that a method using the principle of overdrive suppression combined with a study

of spontaneously discharging pacemakers might provide new insight into mechanisms by which drugs affect pacemaker activity. Studies of drug effects on overdrive suppression have been performed in man (Edelist, Langendorf, Pick & Katz, 1963; Castellanos, Lemberg, Sommer & Berkovits, 1965) and in unanaesthetized dogs with surgically-induced heart block (Yormak, Killip, Levitt & Roberts, 1965; Killip, Yormak, Ettinger, Levitt & Roberts, 1966). However, these researches were limited in scope and the present investigation was undertaken to establish overdrive suppression as a method to study systematically drug effects on pacemaker activity. For this purpose, isolated perfused cat hearts with surgically-induced heart block were employed. In this preparation the effects of drugs on both overdrive suppression and the intrinsic activity of the atrial and ventricular pacemakers could be determined in the same experiment. In the present study the effects of the beta adrenoceptor antagonists propranolol and practolol were investigated. Practolol was used in the form of the racemate while propranolol was used in the form of the racemate as well as the (+)- and (−)-isomers.

A preliminary account of some of this work has been given (Kelliher & Roberts, 1970).

Methods

Cats, weighing between 2 and 3 kg, were rendered unconscious with maximal electric shock while being ventilated with 100% oxygen through a cannula inserted into the trachea under local anaesthesia (procaine). Heparin (1,000 USP units) was injected into a femoral vein prior to the electric shock. After opening the chest, a cannula was inserted into the aorta and the heart was removed and perfused according to the method of Langendorff with Krebs-Ringer solution bubbled with 95% O_2–5% CO_2. The solution contained (mM): Na^+, 145; K^+, 5·8; Ca^{++}, 1·1; Mg^{++}, 1·2; Cl^-, 127; HCO_3^-, 25; SO_4^{--}, 1·2; PO_4^{--}, 1·2; glucose, 5·6.

The temperature of the perfusion fluid was maintained at 37° C by appropriate thermoregulation of the water jacket. The pH, pO_2 and pCO_2 of perfusion fluid was monitored throughout the experiment. The pH ranged between 7·38–7·44, pO_2 between 600–700 mmHg and pCO_2 between 28–30 mmHg (1 mmHg≡1·333 mbar). The coronary arteries were perfused at a constant rate of 25 ml/min by passing the perfusion fluid through a constant rate infusion pump. Perfusion pressure was kept constant at 60 cm H_2O.

Stainless steel recording electrodes were sewn onto the right and left atrium and left ventricle. The electrogram was recorded on a direct writing polygraph. Complete heart block was produced by using a modification of the method of Grumback (1956). The right atrium was opened to visualize the bundle of His and complete heart block was produced by ligating the bundle. Bipolar stainless steel stimulating electrodes were placed on the base of the left ventricle.

The amount of drug used is expressed in terms of the free base. The total dose administered up to any given time was determined by calculating the total volume of the perfusion fluid applied to the heart during the specified time period and then multiplying this volume by the concentration of the drug in the perfusion fluid. The deadspace (125 ml) was taken into account in these calculations.

The pacing rate of the ventricle was set at a frequency two-thirds greater than the initial idioventricular rate. The ventricle was paced for 2 min once every 10 min throughout the duration of the experiment. If the ventricle is paced more

frequently or at higher rates, the intrinsic rate of the ventricle diminishes and as a consequence the asystolic period following pacing progressively lengthens. To diminish the influence that changes in heart rate occurring during the course of experiment (due to spontaneous or drug-induced alterations) may have on overdrive suppression, the idioventricular rate was determined before each pacing period and the stimulus pacing rate was adjusted to be two-thirds greater than this rate. The intensity of the pacing stimulus was just above threshold; a Grass S5 stimulator was used to pace the ventricle.

Overdrive suppression was measured by the interval (ODI) between the last response evoked by artificial stimulation and the initiation of the first intrinsic beat. It was ascertained that this interval would remain relatively constant for periods up to 80 min after the control interval was determined. In all cases, drug administration was not initiated until 3 successive ODI's were within 3–5% of each other.

The effect of drugs on the intrinsic rate of the atrial or ventricular pacemaker was determined from the electrogram; a 5 s interval was employed for this purpose. (±)-Propranolol and the (+)- and (−)-isomers were perfused in concentrations of 400 μg/l. while practolol was infused in concentrations of 50 mg/litre.

In some animals reserpine (5 mg/kg) was injected intraperitoneally 24 h before the experiment.

Results

Stability of the preparation

The reproducibility of ODI was examined in 4 preparations and it was found that after the control ODI was established (see **Methods**), the magnitude of ODI remained relatively constant for approximately 80 minutes. A 7% increase in ODI was the maximum variation which occurred during this time. After 80 min, however, the preparation in some cases began to change rapidly and within a 30 min period increases or decreases amounting to 25–30% of control spontaneously occurred. Thus, to avoid effects due to such spontaneous changes, drug actions were determined within a 60 min period. It should be emphasized that washout of the drug occurred in part during the unstable intervals and the results obtained during this time must be considered somewhat tenuous.

In the absence of drugs, atrial and ventricular rates remained constant throughout the course of an experiment, i.e. up to 90–120 minutes. Nye & Roberts (1966a) have reported in isolated cat hearts with heart block that atrial and ventricular rates remain relatively constant for periods up to 4 hours.

Effect of (±)-propranolol on atrial and ventricular rates

Propranolol did not significantly influence the rate of the atrial pacemaker at any of the cumulative doses obtained (Fig. 1). However, a significant depression of the ventricular pacemaker was achieved at a cumulative dose of 300 μg; the maximal depression in rate was approximately 22% and occurred at a cumulative dose of 600 μg. The depressant effect on the ventricular pacemaker appeared to be reversible since after 25 min of washout, i.e. between 80–90 min (taking into account the dead space), the ventricular rate was reduced only 10% below the ventricular rate obtained just prior to the perfusion of propranolol.

It is interesting to note that when quinidine is administered to the isolated cat heart effects directly opposite to those of propranolol were obtained (Nye & Roberts, 1966a). The atrial pacemaker was more sensitive to the depressant action of the drug than the ventricular pacemaker.

Effect of (±)-propranolol on overdrive suppression (ODI)

Propranolol caused a significant prolongation of ODI within the first 10 min of perfusion producing a maximum prolongation of approximately 35% at a cumulative dose of 600 μg (Fig. 1). During the washout period ODI became erratic and it was not possible to determine whether the drug effect on this parameter could be reversed.

It should be emphasized that (±)-propranolol produced significant prolongation of ODI at a cumulative dose of 100 μg while it required a cumulative dose of 300 μg to produce significant depression of the ventricular rate. (The atrial rate was not affected at any of the cumulative doses achieved.)

Effect of the (+)-isomer of propranolol on atrial and ventricular rates

Since it has been reported that the (+)-isomer of propranolol produces antiarrhythmic effects similar to those of the racemate (Lucchesi, Whitsitt & Brown, 1966), but is an extremely weak β-adrenoceptor antagonist (Howe, 1963), it appeared desirable to compare its action with that of the (±)-form under the experimental conditions of the present study. The (+)-isomer not only caused slowing of the

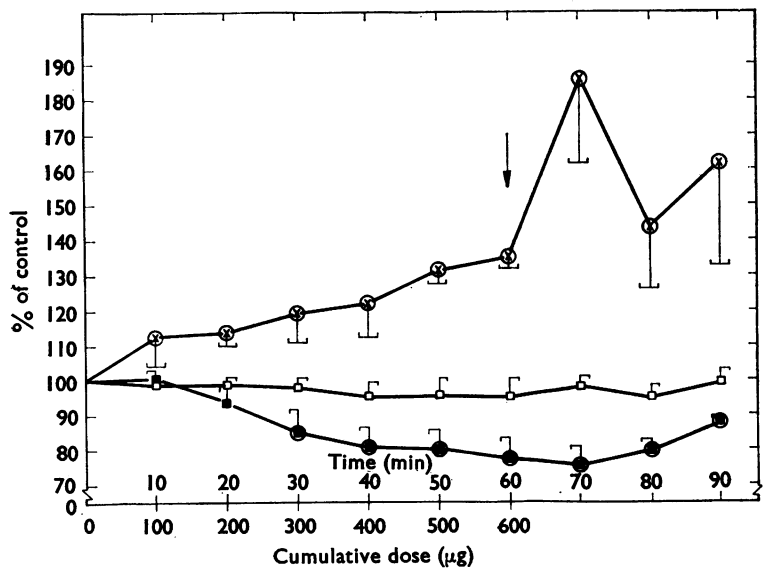

FIG. 1. The effects of (±)-propranolol on atrial (□——□) and ventricular (■——■) rates and overdrive suppression (×——×) in isolated cat hearts with heart-block. Perfusion with (±)-propranolol (400 μg/l.) was initiated at zero time. The arrow marks the end of perfusion with the drug. The control atrial rate was 118·5±6·9 beats/min, the control ventricular rate was 52·8±1·9 beats/min and the control overdrive suppression interval was 1·9±0·1 s (see **Methods** for details). The number of observations was 6. The vertical lines represent the standard error of the mean. The circled values are significantly different from the control ($P<0·05$).

ventricular rate but also depressed the rate of the atrium (Fig. 2). Indeed, a significant effect on the atrial rate occurred after the first 10 min of perfusion; maximum reduction of 20% occurred after a cumulative dose of 600 μg, whereas at the same cumulative dose of the racemate less than a 5% change in atrial rate was achieved.

The effect of the (+)-isomer on the ventricular pacemaker also appeared to be more marked than that of the racemate. The depressant effect of the (+)-isomer occurred much more rapidly, i.e. after only 10 min of perfusion and was more intense; a maximum reduction in rate of 35% was achieved at 600 μg while the racemate produced a maximum reduction of approximately 25% at the same cumulative dose. During the 30 min washout period the atrial or ventricular pacemaker did not appreciably recover from the depressant actions of the (+)-isomer.

Effect of the (+)-isomer of propranolol on overdrive suppression (ODI)

As in the case of the racemate, the (+)-isomer produced significant prolongation of ODI within the first 10 min of perfusion. Maximum prolongation, however, was of a greater order of magnitude than with the (±)-form. The maximum prolongation of ODI produced by the (+)-isomer was approximately 50% whereas that of the racemate perfused at the same concentration was only approximately 35%. During the washout period, it appeared that there was some reduction in the effect of the (+)-isomer since the prolongation of ODI was reduced within 30 min after washout was initiated.

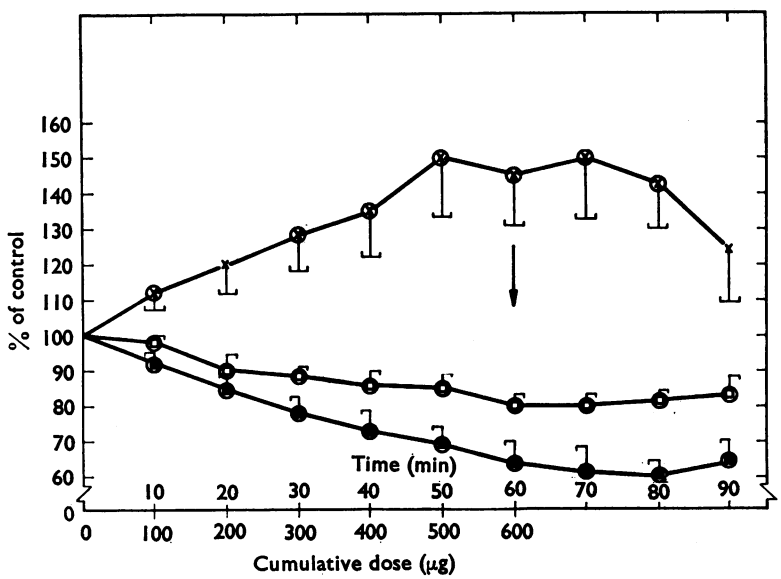

FIG. 2. The effect of (+)-propranolol on atrial (□——□) and ventricular (■——■) rates and overdrive suppression (×——×) in isolated cat hearts with heart-block. Perfusion with the (+)-isomer (400 μg/l.) was initiated at zero time. The arrow marks the end of perfusion with the drug. The control atrial rate was 136·7±5·1 beats/min, the control ventricular rate was 53·5±5·8 beats/min and the control overdrive suppression interval was 1·8±0·3 s (see **Methods** for details). The number of observations was 4. The vertical lines represent the standard error of the mean. The circled values are significantly different from the control ($P<0·05$).

Effect of the (−)-isomer of propranolol on atrial and ventricular rates

It has been reported that the (−)-isomer of propranolol is not only a more potent β-adrenoceptor antagonist than the (+)-isomer but is also a more potent anti-arrhythmic agent (Barrett & Cullum, 1968; Dohadwalla, Freedberg & Vaughan Williams, 1969). In the present experiments the (−)-isomer was more potent than either the (+)-isomer or the racemate in depressing the atrial or ventricular pacemakers. Depression of the atrial rate developed abruptly after 40 min of perfusion and the atrial pacemaker ceased functioning when a cumulative dose of 500 μg had been perfused (Fig. 3). At this same cumulative dose the racemate had reduced the atrial rate less than 5% while the (+)-isomer had reduced the atrial rate less than 15%. The ventricular pacemaker was also more severely depressed by the (−)-isomer than by the racemate or (+)-isomer; a reduction in rate of approximately 52% was achieved when a cumulative dose of 600 μg was reached. Recovery from drug effect did not occur during a 30 min washout period (Fig. 3).

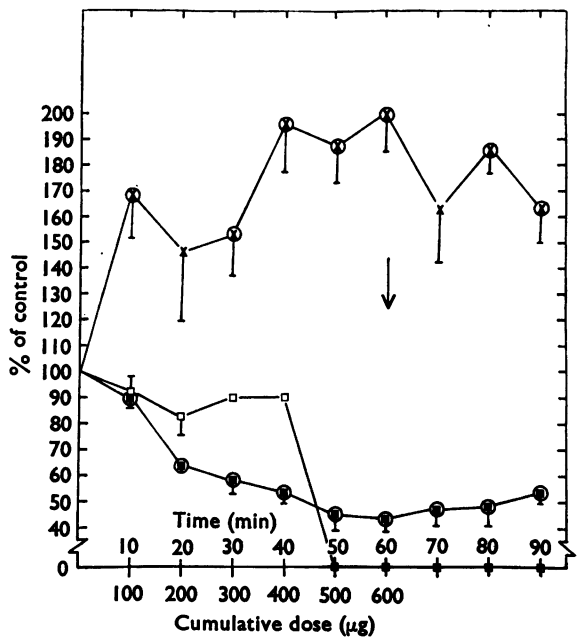

FIG. 3. The effect of (−)-propranolol on atrial (□——□) and ventricular (■——■) rates and overdrive suppression (×——×) in isolated cat hearts with heart-block. Perfusion with (−)-isomer (400 μg/l.) was initiated at zero time. The arrow marks the end of perfusion with the drug. The control atrial rate was 120·0±5·0 beats/min, the control ventricular rate was 43·5±5·3 beats/min and the control overdrive suppression interval was 1·9+0·2 s (see **Methods** for details). The number of observations was 4. The vertical lines represent the standard error of the mean. The circled values are significantly different from the control ($P<0·05$).

Effect of the (−)-isomer of propranolol on overdrive suppression (ODI)

The (−)-isomer of propranolol caused a rapid and marked prolongation of ODI. Indeed, within 10 min of perfusion a prolongation of ODI of approximately 70% occurred. This was the largest effect produced by any of the stereoisomers perfused over this interval. At a cumulative dose of 600 μg a prolongation of ODI of approximately 100% occurred. The maximum prolongation produced by the

(+)-isomer and the racemate was approximately 50 and 40% respectively. As was the case during the washout of the effects of the racemate, the response became erratic and it was not possible to determine whether the drug effect could be reversed.

The effect of (−)-propranolol on ODI was more marked than the effects on the rate of either the atrial or ventricular pacemaker. While after 10 min of perfusion with the (−)-isomer ODI was markedly affected, the atrial rate was not significantly reduced and the ventricular rate fell by 10%.

Effect of practolol on atrial and ventricular rates

Practolol is a β-adrenoceptor antagonist which has been reported to exert a selective blocking action on the β-adrenoceptors of the heart (Dunlop & Shanks, 1968). It has also been shown to exert weak quinidine-like depressant effects on the cardiac muscle (Papp & Vaughan Williams, 1969; Kelliher & Roberts, 1970). Thus, it differs significantly in its actions from propranolol and its isomers. The results of the present study also suggest that there are significant differences between practolol and propranolol and its isomers.

Practolol was infused in a concentration of 50 mg/l. since at concentrations ranging between 24–100 mg/l. quinidine-like changes in the transmembrane action potential of isolated rabbit atria are produced (Papp & Vaughan Williams, 1969; Kelliher & Roberts, 1970). However, even in this very large concentration practolol did not produce depression of the atrial or ventricular pacemaker rates but in fact caused a rapid and striking increase in the rates of both these pacemakers (Fig. 4).

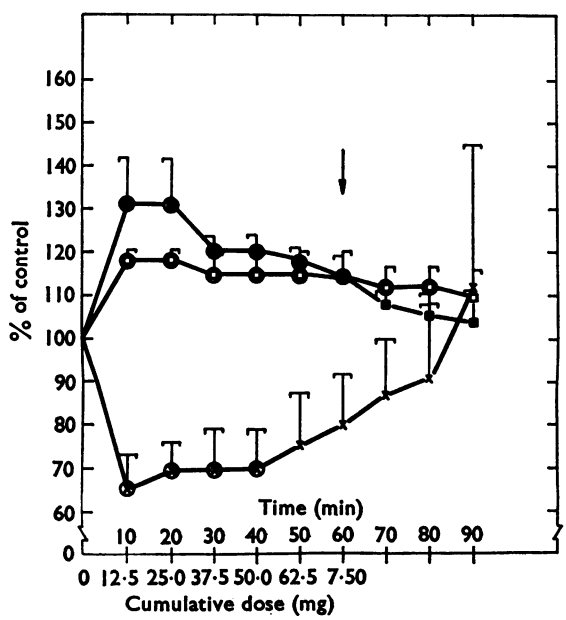

FIG. 4. The effect of practolol on atrial (□——□) and ventricular (■——■) rates and overdrive suppression (×——×) in isolated cat hearts with heart-block. Perfusion with practolol (50 mg/l.) was initiated at zero time. The arrow marks the end of perfusion with the drug. The control atrial rate was 128·0±5·0 beats/min, the control ventricular rate was 54·7±5·8 beats/min and the control overdrive suppression interval was 1·6±0·2 s (see **Methods** for details). The number of observations was 4. The vertical lines represent the standard error of the mean. The circled values are significantly different from the control ($P<0·05$).

The maximal effect on both pacemakers occurred within 10 min after the initiation of perfusion; the atrial rate increased approximately 18% while the ventricular rate rose approximately 30%. Perfusion with normal Krebs-Ringer after 60 min of perfusion with the drug seemed to wash out the effect of the drug on the ventricular pacemaker but not that on the atrial pacemaker.

Atrial and ventricular rates in reserpine-treated hearts

To determine whether the increase in atrial and ventricular rates was due to intrinsic activity of the compound or to catecholamine release the effect of practolol was tested in isolated hearts removed from cats pretreated with reserpine (5 mg/kg, i.p.) 24 h before the experiment. Nye & Roberts (1966b) found that reserpine-pretreatment does not influence the rate of atrial or ventricular pacemakers in isolated hearts. Similar results were obtained in the present study. In reserpine-pretreated hearts from 4 cats the average atrial rate was $119{\cdot}3 \pm 14{\cdot}6$ beats/min while the average ventricular rate was $40{\cdot}5 \pm 6{\cdot}4$ beats/minute. These rates closely parallel those found in the 18 hearts without reserpine (Figs. 1, 2, 3 and 4). The perfusion of reserpine-treated hearts with practolol (50 mg/l.) continued to result in an acceleration of both atrial and ventricular rates (Fig. 5). Indeed, the percentage increases in rate were even slightly higher in the reserpine-treated hearts, i.e. atrial rate increased approximately 23% and the ventricular rate rose approximately 42%.

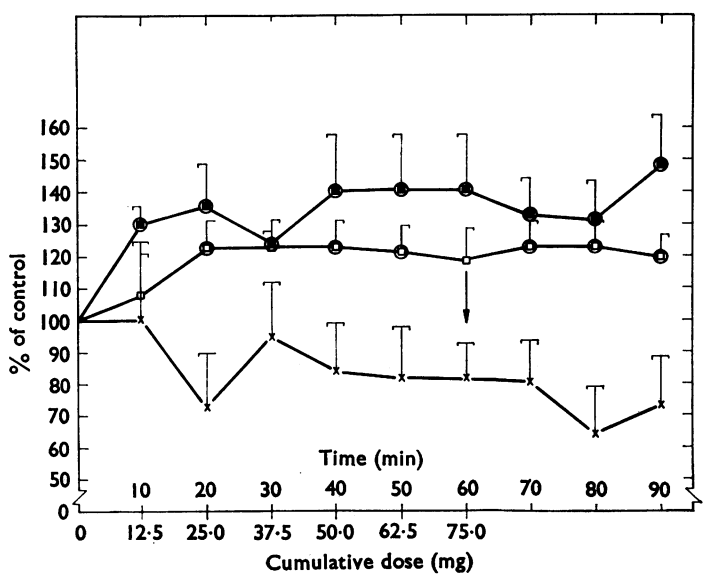

FIG. 5. The effect of practolol on atrial (□——□) and ventricular (■——■) rates and overdrive suppression (×——×) after reserpine-pretreatment in isolated cat hearts with heart-block. Reserpine (5 mg/kg) was administered intraperitoneally 24 h before the experiment. Perfusion with practolol (50 mg/l.) was initiated at zero time. The arrow marks the end of perfusion with the drug. The control atrial rate was $119{\cdot}3 \pm 14{\cdot}6$ beats/min, the control ventricular rate was $40{\cdot}5 \pm 6{\cdot}4$ beats/min and the control overdrive suppression interval was $2{\cdot}6 \pm 0{\cdot}4$ s (see **Methods** for details). The number of observations was 4. The vertical lines represent the standard error of the mean. The circled values are significantly different from the control ($P<0{\cdot}05$).

Effect of practolol on overdrive suppression (ODI)

Practolol did not cause prolongation of ODI even when perfused at high concentrations (50 mg/l.): a significant decrease in ODI occurred (Fig. 4). Maximum effects developed within 10 min after the initiation of perfusion and ODI was reduced by approximately 35% at this time. This effect did not persist throughout the 60 min of perfusion, however, and at the end of the perfusion period, there was no significant effect on ODI.

Overdrive suppression in reserpine-treated hearts

Reserpine pretreatment caused a prolongation of ODI from that seen in hearts not pretreated with reserpine. In 4 reserpine-treated hearts ODI was on the average $2{\cdot}6 \pm 0{\cdot}4$ s while in 18 non-reserpine treated preparations it was on the average $1{\cdot}8 \pm 0{\cdot}2$ s ($P<0{\cdot}05$). The most significant finding was, however, that in reserpine-pretreated hearts practolol did not significantly influence ODI throughout the entire period of perfusion (Fig. 5). This finding is in sharp contrast to the effect of practolol in hearts not pretreated with reserpine since in these hearts practolol shortened ODI by approximately 35%. The data suggest that catecholamines play an important role in the action of practolol on ODI.

Discussion

One of the principal aims of this study was to determine whether overdrive suppression was a suitable method to determine drug action on pacemaker sites. The results of the study clearly indicate that the overdrive suppression interval (ODI) can be used for this purpose and indeed may be an even more sensitive indicator of the reactivity of pacemakers to drugs than the intrinsic rate of pacemakers. With (±)-propranolol, prolongation of ODI occurred at dose levels which did not affect the intrinsic rate of either the atrial or ventricular pacemakers. With both the racemate and the (+)- and (−)-isomers the maximum effect of the drug was always greater on ODI than on the intrinsic rate of the atrial or ventricular pacemaker and in most cases the effect on ODI developed more rapidly.

It appears that in the ventricle, overdrive suppression results from the development of an increased sodium load in pacemaker cells (Vassalle, 1971). This increased sodium load activates an electrogenic extrusion of sodium which shifts diastolic depolarization to a more negative value. When the stimulus driving the pacemaker is terminated, the diastolic depolarization levels of the intrinsic pacemaker remains at a value negative with respect to its threshold potential until the electrogenic extrusion of sodium ceases or is suitably reduced. Thus, if an agent prolongs ODI it is probable that the agent depresses the system which decreases the sodium load. On the other hand, depression of the firing rate of the ventricular pacemaker would largely depend on the effect of a drug on potassium flux; it is generally thought that diastolic depolarization in pacemaker tissue is caused by a time-dependent decrease in potassium efflux (Vassalle, 1971). It appears that examining drug effects on overdrive suppression and intrinsic rhythmicity of pacemakers may provide different indicators of drug action on pacemaker function.

While reserpine did not affect the intrinsic rate of the pacemakers of the isolated heart, it did prolong ODI. This suggests that catecholamines are involved in the overdrive suppression process. If ODI is dependent on the time to decrease the

sodium load, then perhaps catecholamines provide a stimulus for this system. It has been shown that adrenergic activity increases the rate of diastolic depolarization (Hutter & Trautwein, 1956), and enhances the current flow due to Na^+ and Ca^{++} during the plateau of the transmembrane action potential (Vassort, Rougier, Garnier, Sauviat, Coraboef & Gargouil, 1969). Thus, it is possible that in the absence of catecholamines it would require longer periods to establish a normal sodium relationship. That adrenergic influences may be involved in overdrive suppression is also suggested by the greater potency of the (−)-isomer of propranolol than the (+)-isomer in prolonging ODI. It has been shown that the (+)-isomer of propranolol is about equally effective or slightly less potent than the (−)-isomer as an antiarrhythmic agent but as a β-adrenoceptor blocking agent it is only 1/40 as potent as the (−)-isomer (Lucchesi *et al.*, 1966; Dohadwalla *et al.*, 1969; Barrett & Cullum, 1968).

The ability of reserpine to prolong ODI is probably not related to a direct depressant action. It has been shown that unlike quinidine, reserpine does not cause changes in the transmembrane action potential or fluxes of sodium and potassium (Vaughan Williams, 1958; Spilker & Cervoni, 1969; Choi & Roberts, 1970).

Since the racemate is only 50% (−)-isomer and the remainder represents the less potent (+)-isomer, it is not surprising that the (−)-isomer proved to be more potent in prolonging ODI than the racemate. (Similar potency relationship exists in the effects of the isomers on slowing the atrial or ventricular rate.) However, the greater effectiveness of the (+)-isomer relative to the racemate is unexpected since on the basis of the potency relationship of the (−)- to the (+)-isomer, the racemate should have been more potent than the (+)-isomer as 50% of the effect of the racemate is due to the (−)-isomer. Similar results with the (+)- and (−)-isomers were reported by Barrett & Cullum (1968). They noted that the (+)- and (−)-isomers were more potent local anaesthetics than the racemic mixture. The interaction between the (+)- and (−)-isomers of propranolol which causes the racemate to be less potent than the (+)-isomer may involve distribution of the (−)-isomer to the site of action. It has been reported previously that the uptake of catecholamines into storage granules exhibits stereospecificity (Stjarne & von Euler, 1965). More recently Sugrue & Shore (1971) have suggested that there is a sodium-dependent optically specific carrier mechanism at all adrenergic neurones. It is possible then, that distribution of propranolol to its site of action is also stereospecific. If this is the case, then the (+)-isomer might interfere with the uptake of (−)-isomer. Kaplan, Lasala & Robson (1971) reported results which indicate that both stereoselective and non-stereoselective mechanisms have significance in the activity and biological disposition of the beta adrenoceptor blocking agent, bunolol, and its optical isomers.

The present results support the finding that practolol does not readily cause direct depression of cardiac muscle (Dunlop & Shanks, 1968; Papp & Vaughan Williams, 1969 and Kelliher & Roberts, 1970). The action of practolol was found to be entirely different from the action of propranolol and its isomers. Even in extremely large concentrations (50 mg/l.) practolol shortened ODI. This action was absent after reserpine and so may involve the release of catecholamines. Practolol enhanced the activity of both atrial and ventricular pacemakers. This action is apparently due to a direct effect since it is not influenced by catecholamine depletion. Although Papp & Vaughan Williams (1969) and Kelliher & Roberts (1970)

using concentrations of practolol comparable to those used in the present study (50 mg/l.) were able to demonstrate quinidine-like activity on the transmembrane action potential of the rabbit atria, the effect on pacemaker tissue is unlike that produced by quinidine. Quinidine in isolated cat hearts with heart-block causes striking depression of both the atrial and ventricular pacemaker (Nye & Roberts, 1966a).

Since practolol apparently does not cause depression of cardiac tissue activity, its reported effectiveness against digitalis-induced arrhythmias must be due to other actions (Papp & Vaughan Williams, 1969; Kelliher, Levitt, Raines & Roberts, 1971). Roberts, Ito, Reilly & Cairoli (1963) and Roberts, Levitt & Standaert (1967) previously reported evidence which suggests a role for the sympathetic nervous system in the genesis of digitalis-induced arrhythmia. Papp & Vaughan Williams (1969) suggested that practolol may act like bretylium in depressing adrenergic nerve terminals. It is possible, therefore, that practolol, by preventing the action of digitalis on sympathetic nerves, reduces the capacity of digitalis to produce arrhythmia. In any case since the antiarrhythmic activity of practolol is not associated with marked cardiac depression, it could be superior to propranolol in the treatment of digitalis-induced arrhythmias.

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