RECENT ADVANCES IN PHARMACOLOGY

FOURTH EDITION

by

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PREFACE

New editions of *Recent Advances in Pharmacology* have, in the past, always been new books: the same is true of this edition. Subjects are selected in which considerable developments have occurred in the preceding years and such is the rate of development that even where the same topic appears in successive volumes, the chapter needs to be completely re-written and in fact is often complementary to the preceding one. Of the nineteen topics in the present volume only those on catecholamines and polypeptides are in this category and the developments in these subjects during the six years since the third edition clearly warrant their presence in this volume.

In the last edition an innovation was introduced in that the editors no longer sought to cover the whole field themselves but invited the co-operation of experts in particular fields. In the present edition this process has been carried to the limit and all chapters have been contributed by invitation, although our original intention was to make a substantial contribution ourselves. However, in order to keep the book to reasonable dimensions, it has been necessary to exclude a number of topics which well deserved a place. In making our selection, we have endeavoured to cover a wide field, extending into neighbouring sciences in the hope that the fields so established will be of interest and value.

We wish to express our thanks to those authors and publishers who have permitted us to reproduce published figures, to Miss Anne Miller for her valuable help with the manuscript and to Mr. J. A. Rivers of Messrs. J. & A. Churchill Ltd. for his continued co-operation.

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CHAPTER 1

DRUGS AND EXCITABLE CELL MEMBRANES

GENERAL PRINCIPLES

Excitable tissues are those which show a recognizable physiological response to mechanical, electrical or chemical stimulation, and include muscles, nerves and glands. Drugs affect their excitability either directly or more often by interfering with the stimulation of one set of cells by another. Impulses are relayed from nerve endings to muscles or glands, or to other nerve cells, by the familiar process of humoral transmission. The climax of the process is the excitation, or sometimes inhibition, of the recipient cell by the transmitting agent. In many circumstances, but not in all, this agent is acetylcholine. Many pharmacological actions result from interference with the action of transmitters on recipient cells. Tubocurarine prevents the excitatory action of acetylcholine on motor end plates of skeletal muscle. Atropine prevents the excitatory action of acetylcholine on intestinal smooth muscle, and also the inhibitory action of acetylcholine on cardiac pacemaker tissues. Suxamethonium and decamethonium each stimulate motor end plates as acetylcholine does, but after stimulation the muscle becomes paralysed and unresponsive for a time to nerve impulses or to injected acetylcholine. Hexamethonium blocks autonomic ganglia, and the close similarity of its chemical structure to that of decamethonium suggests that it might act in an analogous way. It does not, however, stimulate ganglia before blocking them, whereas a structurally quite different substance, nicotine, stimulates and then paralyses ganglia, much as decamethonium acts on motor end plates.

These processes are made clearer by measuring the associated electrical events in the tissues. When a sufficiently small electrode is pushed through a cell wall into the interior, and the potential difference is measured between the inside of the cell and the surrounding fluid, the inside is usually negative to the outside by 50–100 millivolts. When an excitatory transmitter is applied to a sensitive membrane, for instance acetylcholine to a motor end plate, the polarity disappears. Depolarization of a motor end plate is followed by the outward spread of a wave of depolarization across the whole muscle cell membrane, and depolarization of the membrane is followed by contraction of the myofibrils. Depolarization of the synaptic membrane of a nerve initiates in the adjacent membrane a similar disturbance which is then propagated along the nerve fibre. At the nerve terminal the arrival of the wave of depolarization starts events which lead to release of the next transmitter substance.

When a transmitter has inhibitory effects, such as acetylcholine has on cardiac pacemaker cells, the resting membrane potential is generally

altered in the opposite direction, i.e. the transmitter hyperpolarizes, or makes the inside more negative to the exterior than before. This disturbance is not propagated and remains as a local effect, rendering the excitable region less sensitive to the normal action of excitatory transmitters (such as catecholamines at the pacemaker) or to electrical stimulation.

Blocking agents, such as the methonium compounds, or tubocurarine or atropine, act in one of two ways, either preventing or promoting depolarization. Tubocurarine is an anti-depolarizing blocking agent, preventing depolarization induced by acetylcholine and the usual sequel of muscular contraction. Decamethonium, on the other hand, depolarizes and remains at its site of action so that the depolarization persists. An impulse is propagated by the depolarization, and may cause an initial twitch of the muscle. As long as the end plate remains depolarized, no further disturbance can be propagated, and the muscle remains paralysed to all stimuli except those acting directly on the contractile mechanism.

It is possible to discuss these and similar events in terms of 'receptors', undefined substances or structures in or on the cells, which are activated or inhibited by the agents concerned. Receptor theories (see Chapter 4) permit much quantitative refinement (Stephenson, 1956; Ariens, van Rossum & Simonis, 1957) and are particularly useful in studying antagonists (Arunlakshana & Schild, 1959; Paton, 1961), but the theories run into difficulties of detail with systems as complex as cell membranes. Antagonists of one kind are supposed to antagonize by combining with the same receptors as the agonist (or active substance), either stimulating as they do so or not. Such antagonists are usually described as competitive with the agonist because both kinds of molecule compete for the same receptors. Alternatively an antagonist may act at a later stage in a sequence of events, and block the process initiated by an agonist. Such blocking is clearly not competitive in the receptor sense, even though theoretically at least partial block at an advanced stage of a sequence of events might be overcome by sufficiently powerful stimulation at an earlier stage. Application of receptor theory to drugs acting on the motor end plate has had the unfortunate consequence of labelling tubocurarine and gallamine 'competitive antagonists' and suxamethonium and decamethonium 'non-competitive antagonists', although, as Taylor & Nedergaard (1965) have pointed out, there is good reason to regard the methonium compounds rather than the antidepolarizers as 'competitors' with acetylcholine. Moreover, the distinction between types of blocking agent at motor end plates is far from absolute. The methonium compounds sometimes act as antidepolarizing agents and vice versa (Paton & Waud, 1962) and additional facts about the relevant variables are essential in order to describe the responses quantitatively.

It is more helpful to consider what is known of the structure and function of excitable cell membranes in order to interpret how transmitters and other excitants act and how blocking agents interfere with the pro-

cesses (Table 1). The structure of cell membranes, in terms of the exact compounds which constitute them and the precise spatial arrangement of these compounds is at present known only in an approximate and speculative way. Indeed, the notion of any cell as a closed bag of cytoplasm is often too simple to be useful. Most contemporary ideas about excitable membranes are derived from quantitative observations on giant nerve fibres of marine invertebrates, which have axons particularly suitable for

Table 1

Variables affecting excitability of cells

Species of animal	
Tissue from which cell is derived	
Temperature	
pH of surrounding medium	
Concentration of sodium in surrounding medium	$[Na^+]_o$
,, ,, potassium ,, ,,	$[K^+]_o$
,, ,, calcium ,, ,,	$[Ca^{2+}]_o$
,, ,, chloride ,, ,,	$[Cl^-]_o$
,, ,, other electrolytes ,,	
,, ,, sodium in cytoplasm	$[Na^+]_i$
,, ,, potassium ,,	$[K^+]_i$
,, ,, chloride ,,	$[Cl^-]_i$
,, other electrolytes in cytoplasm	
Metabolism of cells, depending on temperature, availability of metabolites (often especially oxygen and dextrose), absence of enzyme poisons.	
State of cell membrane, depending on resting membrane potential and absence or presence of substances affecting permeability.	
Note that the variables below the line are complex functions of, among other things, the more elementary variables listed above the line.	

the insertion of micro-electrodes. Also the cytoplasm can be expressed from their tubular interior and be analysed, or replaced by artificial fluids (Baker, Hodgkin & Shaw, 1962a, b; Baker, Hodgkin & Meves, 1964), so that both internal and external aspects of the membrane can be controlled. The interior of muscle cells is vastly more complicated. Its organized structure may include an endoplasmic reticulum which is perhaps an inward extension of the cell membrane and capable of transmitting changes of polarity to sites deep within the cell structure. By the time a muscle cell has been filled with myofibrils, mitochondria, a nucleus and other inclusions, there is not much room left for liquid 'myoplasm', nor much opportunity for any myoplasmic constituents to be freely diffusible within the cell (cf. Taylor, Dixon, Creese & Case, 1967). The fact remains that electrodes have been introduced into many varieties of muscle cells and potentials have been recorded, in many ways similar to those obtained from nerve fibres. Muscles are more complex, but the basic mechanism of excitability is evidently similar in muscle and in nerve.

THE IONIC BASIS OF ELECTRICAL ACTIVITY IN TISSUES

THE RESTING MEMBRANE POTENTIAL

The process has been described in detail in reviews (Hodgkin, 1951; Hodgkin, 1958; Huxley, 1959; Katz, 1966) and text books. Extracellular fluids contain relatively high concentrations of sodium and chloride and low concentrations of potassium, whereas intracellular fluids contain much potassium, little sodium and chloride, and the positive charges of the potassium ions are neutralized partly by large molecules with negative charges, including phosphate esters and peptides. Concentration gradients therefore occur across the cell membrane and if unopposed would result in outward movement of potassium and of large anions and in inward movement of sodium and chloride. The large anions do not escape from the cells and may be assumed to be too large to penetrate the membrane or to be anchored to the cell structure. The cell membrane is moderately permeable to potassium and chloride and at rest rather less so to sodium, as can be shown by adding radioactive tracers to the extracellular medium and measuring their rate of uptake by the tissue (Harris & Burn, 1949; Keynes & Lewis, 1951). The uneven distribution of potassium and chloride can be attributed partly to the fixed anions, which produce some part of the negative intracellular resting potential. That is, the electrical potential gradient opposes the chemical concentration gradient for each ion species. Often the two forces can be shown to be approximately in equilibrium, because the chloride ratio and potassium ratio are both close to the theoretical value which can be calculated for a given membrane potential, as discussed later (p. 5). The situation for sodium is more complex, because potential and chemical gradients both drive sodium into cells, but the intracellular concentration of sodium nevertheless remains low in healthy tissues. Any impairment of metabolism, e.g. by cooling or by any of numerous poisons such as iodoacetate or dinitrophenol, results in an increase of cell sodium, i.e. failure to maintain the normal low concentration, so it is inferred that sodium is normally extruded against the electrochemical potential gradient by a metabolically driven process, always described as the 'sodium pump'.

Except that it is metabolically driven, the mode of action of this pump is uncertain. If it extruded only sodium ions, each ion extruded would leave a charge equal to one electron within the cell and so contribute to the negative resting potential. If the pump extruded sodium and an anion, say chloride, or if it carried sodium outwards in exchange for another cation, say potassium which was moved inwards, it would be electrically neutral. Stopping the pump, e.g. with dinitrophenol (Hodgkin & Keynes, 1955) does not immediately alter the membrane potential. This evidence does not exclude an electrogenic effect of the pump because the already accumulated excess of negative charges inside the cell will continue to maintain a potential for some time until the system gradually runs down

by leakage at the membrane. The resting membrane potential is too large to be attributable entirely to fixed anions (Falk & Gerard, 1954) and it is difficult to avoid concluding that part of the potential is due to an electrogenic sodium pump.

The forces due to the charges of the ions and those due to concentration gradients are directly related to each other. For a single ion species, say potassium, the potential difference, E_K, between solutions of concentration $[K_o]$ and $[K_i]$ respectively separated by a junction permeable to these ions is given by the equation (Nernst, 1889; cited by Bernstein, 1902)

$$E_K = \frac{RT}{F} \log_e \frac{[K_o]}{[K_i]}$$

where R is the gas constant (1·99 calories per mole per degree C.), T the absolute temperature, F Faraday's constant (96,500 coulombs per gramme-equivalent) and the sign of the potential refers to the side with concentration $[K_i]$. The potential E_K so calculated indicates the work necessary to produce the concentration difference despite the permeability of the barrier. Alternatively, if the ions diffuse through the barrier towards equal concentrations, E is the potential at which energy is initially released in the running-down process.

In physiological situations, several ion species are involved, and the barrier between the inside and outside solutions has a limited and distinct permeability to each ion species. The relationship between concentrations, permeabilities and potential most used in this more complex situation is due to Goldman (1943) and is as follows:

$$E = \frac{RT}{F} \log_e \frac{P_{Na}[Na_o] + P_K[K_o] + P_{Cl}[Cl_i]}{P_{Na}[Na_i] + P_K[K_i] + P_{Cl}[Cl_o]}$$

where P_{Na}, P_K and P_{Cl} are permeability constants for the respective ions and the other terms have meaning as before. The Goldman equation reduces exactly to that of Nernst if P_{Na} and P_{Cl} are both zero, i.e. if the membrane is treated as impermeable to both sodium and chloride. As long as P_{Na} and P_{Cl} are small compared with P_K, the equilibrium potential calculated by the Goldman equation does not differ much from that given by the Nernst equation. Moreover, the ratio $[K_o]/[K_i]$ is in many tissues fairly close to the ratio $[Cl_i]/[Cl_o]$, so P_{Cl} can become as large or larger than P_K with little alteration in the estimated membrane potential.

The ratio of concentrations of sodium ($[Na_o]/[Na_i]$), however, is in the opposite direction. For the resting membrane potential to be negative, as it in fact is, the numerator of the part of the equation containing the permeability terms must be smaller than the denominator (so that the whole fraction is less than unity and its logarithm negative). The quantities $[K_o]$ and $[Cl_i]$, both of which appear in the numerator, are of the order of 5 and perhaps 10 mM respectively, whereas $[Na_o]$ is at least 140 mM and $[Na_i]$ much smaller than $[Na_o]$. It follows that at rest P_{Na}

must be considerably smaller than P_K or P_{Cl}, in order to give a realistic value for the membrane potential. That P_{Na} is in fact smaller is shown by appropriate measurements of isotopic sodium and potassium in suitable tissues.

EXCITATION AND PROPAGATION

Excitation involves a change in the membrane so that the permeability to sodium ions is suddenly increased. The change can be initiated if sufficient electrical stimulus is applied to reduce the membrane potential below a critical value, about -40 to -50 millivolts. At this potential the membrane becomes unstable and its permeability to sodium increases rapidly. Sodium ions flow in, carrying current which depolarizes the membrane still further and overshoots towards a potential determined by the sodium ratio; i.e. that predicted by the Goldman equation when P_{Na} is large and P_K and P_{Cl} relatively small, in contrast to the condition at rest. It should be noted that the flux of sodium ions, though large compared with the resting value, still represents an exceedingly minute quantity of sodium per impulse, as compared with the total number of sodium ions in the cell. In squid fibres, the sodium entry is about 4 p-mole per impulse per sq. cm. of membrane (Keynes & Lewis, 1951). One sq. cm. of membrane encloses about 0·005 cu. cm. of axoplasm, which contains 250,000 p-mole of sodium. The additional sodium makes an infinitesimal difference to the value of $[Na_i]$, even though the entering ions will be initially located in the axoplasm adjacent to the membrane and not dispersed through its entire volume. The important consequence of the influx is due to the charge carried by the ions.

The change in sodium permeability is accompanied by a more gradual increase in permeability to potassium. Initially the sodium effect predominates, and accounts for the upstroke of the action potential. Later, the increase in P_K results in an augmented efflux of potassium ions, carrying current in the opposite direction and restoring the membrane potential towards its resting value. The value of P_{Na} itself depends on the membrane potential, so repolarization by increased P_K contributes to the reduction of P_{Na} and stopping the depolarizing flow of sodium ions. At the end of the action potential the *status quo ante* is restored, except that the cell has lost a small quantity of potassium and gained a small quantity of sodium. These changes are made good in the course of normal metabolism by some small increase in activity of the sodium pump and a balancing uptake of potassium.

Normally depolarization of a region of cell membrane provides an area into which current flows from the adjacent membrane with consequent spread of depolarization. Once initiated, the disturbance is therefore propagated over the whole length of the cell membrane. Initiation of an impulse in physiological circumstances involves one or other of several processes, according to the site involved.

(i) *At synapses and motor end plates* increase of permeability is initiated chemically by a transmitter, typically acetylcholine, released from the relevant nerve endings.

(ii) *In cardiac pacemaker tissue* the membrane is not stable at rest. The potential achieved after repolarization is maintained only for a short time after which it falls (the diastolic prepotential) towards the critical value for increased sodium permeability, and when this is reached a new propagated depolarization occurs, initiating the cardiac impulse. A similar state of repetitive firing can be induced in other cell membranes, e.g. nerve fibres, by altering factors which affect ionic permeability, notably by lowering the concentration of calcium.

(iii) *In sensory end organs* mechanical deformation induces an increased permeability to sodium and so initiates an action potential.

EXCITATION—CONTRACTION COUPLING

When a wave of depolarization spreads across the membrane of a striated muscle cell, the muscle contracts. A muscle cell can also be made to contract by introducing calcium salts inside the fibre by microinjection. No other substance is known to be equally effective although barium salts are nearly as potent (Heilbrunn & Wiercinski, 1947). Depolarization is accompanied by an increased entry of calcium ions (Bianchi & Shanes, 1959). Calcium ions are bound to contractile proteins and activate myosin adenosine triphosphatase so that contraction occurs (Bailey, 1942). The binding is reversible if the surrounding concentration of calcium is reduced, and removal of calcium in this way is essential for relaxation to occur. Calcium ions are selectively and rapidly concentrated by the sarcoplasmic reticulum (Weber, Herz & Reiss, 1964). The dimensions of striated muscle fibres are too large for calcium released from the surface membrane to diffuse through the fibre and cause activation (Hill, 1949) and the quantity of calcium entering the fibre (Bianchi & Shanes, 1959) is less than one calcium ion per myosin molecule, but the T-system of tubules which represents inward penetration of the plasma membrane (Andersson-Cedergren, 1959) probably provides an anatomical basis for the inward spread of electrical excitation (Huxley, 1964). Many detailed aspects of the process remain to be elucidated; for a recent review, Sandow (1965) should be consulted.

The mechanism of contraction of smooth muscle is much less well established than in striated muscle (Needham & Shoenberg, 1964), though the role of calcium as an activator, and probable coupling element, is strongly suggested by its effects on preparations depolarized by high concentrations of potassium (Evans, Schild & Thesleff, 1958; Edman & Schild, 1962). The rate of exchange of calcium in smooth muscle is much higher than in skeletal muscle, and its measurement and interpretation is complicated by the existence of several fractions exchanging at different

rates (Schatzmann, 1961; Bozler, 1963). Increased tension is associated with increased uptake of calcium (Bauer, Goodford & Hüter, 1965). In cardiac muscle the exact behaviour of calcium is also far from clearly established.

Calcium influx is also increased in nerve fibres during activity (Hodgkin & Keynes, 1955), and calcium is essential for neurosecretory processes involved in the release of acetylcholine from nerve endings and adrenaline from chromaffin cells (Harvey & MacIntosh, 1940; Douglas & Poisner, 1962), as well as for the release of adrenergic neurone blocking drugs from tissue stores (Boullin, 1966). Concentrations of ionized calcium inside cells are generally very low, so that inward movements of calcium, like those of sodium, are down the electrochemical potential gradient and require no energy. The subsequent recovery of calcium ions requires special processes for binding and transporting the ions with the performance of work. Both stages are still relatively poorly understood, but both provide crucial activities liable to be influenced by drugs of various kinds.

ONIUM COMPOUNDS

ACETYLCHOLINE

An onium ion is obtained, typically, by substitution of alkyl or more elaborate radicles for all the four hydrogen atoms of the ammonium ion, but the term onium extends also to ions in which other elements form the centre of the ion (e.g. phosphonium, stibonium compounds). The non-nitrogenous onium compounds are of theoretical interest in understanding physicochemical aspects of biological activity (Taylor, 1951), but they have received very little attention in comparison with substituted ammonium salts. Of these, acetylcholine is outstandingly important, because of its action as a transmitter from nerve endings to motor end plates in skeletal muscle, at autonomic ganglia, at parasympathetic nerve endings and probably at some synapses in the central nervous system. Most of the actions of other onium compounds are closely related to those of acetylcholine, and some of them will be discussed subsequently.

At most sites acetylcholine stimulates the cell on which it acts, or, more precisely, it depolarizes the post-junctional cell membrane and so sets up a propagated electrical disturbance. Details of this kind of action have been worked out most fully for motor end plates: and have recently been summarized by Katz (1966). At sympathetic (Paton & Perry, 1953) and parasympathetic (Perry & Talesnik, 1953) ganglia and on some neurones in the central nervous system (Curtis, Phillis & Watkins, 1961) the action of acetylcholine is essentially similar. At parasympathetic endings in smooth muscle acetylcholine depolarizes and initiates contraction. However, the effect is not confined to an action on the membrane potential. When isolated uteri are immersed in saline media in which potassium is substituted for some or all of the sodium and the membrane potential is

consequently reduced nearly to zero (Evans, Schild & Thesleff, 1958), acetylcholine, like several other stimulants of smooth muscle, still causes appreciable contraction of the tissue without alteration of the membrane potential. The process of depolarization is therefore not an essential step in the action of acetylcholine on smooth muscle. In cardiac muscle the action of acetylcholine is at first sight quite different, as it inhibits spontaneous depolarization in the pacemaker and in sufficient concentration increases the resting membrane potential. Possible reasons for this difference between the action on pacemaker tissue and other muscle are discussed later.

In general, acetylcholine increases the permeability of post-junctional membranes to small cations, i.e. sodium, potassium, calcium, ammonium and some quaternary ammonium ions. At motor end plates, the effect on sodium and potassium is equally important. The increase in sodium permeability results in the inward passage of sodium ions (flowing down both the concentration gradient and the electrical gradient, hitherto excluded by the normally very low permeability to sodium of the resting membrane). The increase in potassium permeability limits the depolarization and prevents reversal of polarity at the end plate. The duration of the effect is limited by local enzymic hydrolysis, and destruction of the acetylcholine is accompanied by restoration of the resting permeability and membrane potential. The influx of sodium is probably accompanied by an influx of calcium, and also by release of calcium from intracellular sites with activation of the contractile process. It remains to be discovered how the internal release of calcium occurs. Under normal conditions contraction of striated muscle is much too rapid to be due to diffusion of calcium ions from outside the cell. The slow contraction induced by acetylcholine in smooth muscle in a depolarizing solution, on the other hand, depends on the presence of calcium in the medium and occurs at a speed probably compatible with diffusion of calcium ions through the hyperpermeable cell membrane, or of their displacement, perhaps by sodium, from cationic sites in the membrane.

The action potentials in cardiac muscle follow a complex course, differing in various respects from those in other muscles and differing also in different parts of the heart. At the pacemaker, the spontaneous depolarization which initiates each heart beat is preceded by a slow fall in potential towards the critical threshold at which the action potential 'takes off'. This diastolic prepotential is flattened by acetylcholine, so that it takes longer to reach the threshold (West, Falk & Cervoni, 1956; Trautwein & Dudel, 1958). Higher concentrations of acetylcholine increase the resting potential, so that the diastolic prepotential has further to go before reaching the critical level for firing. In sufficient concentration of acetylcholine, the diastolic prepotential is abolished altogether and the heart is arrested with a hyperpolarized pacemaker. As long as contractions occur, their force is diminished, sometimes very strikingly.

It is questionable whether acetylcholine makes auricles more permeable to sodium at all. Direct measurements of flux with radioactive sodium are unsatisfactory because single fibres are difficult to isolate and complete auricles have a large extracellular space in which diffusion delays are liable to obscure any change in sodium flux associated with beating. The rate of rise of the action potential, indicative of sodium influx, is not

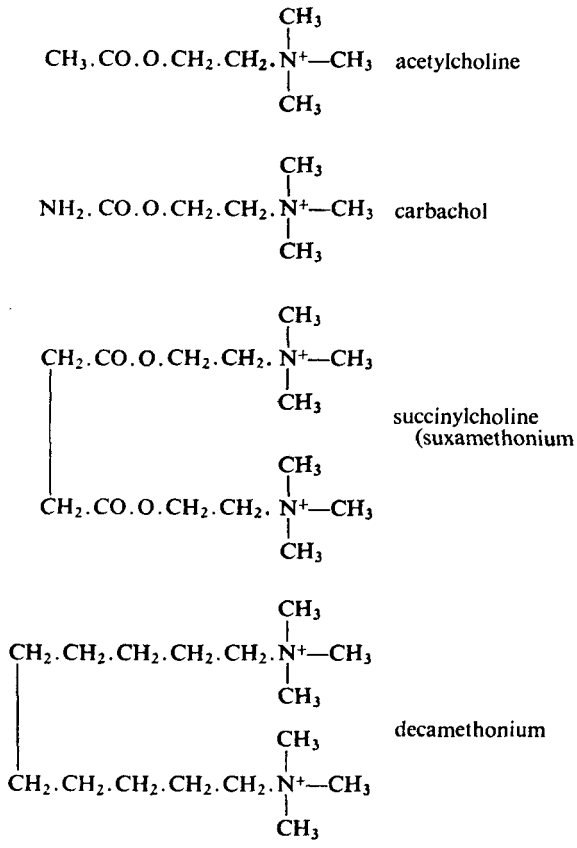

FIG. 1. Onium compounds.

increased, and the rise of the diastolic prepotential is decreased. Sodium and calcium ions probably enter cardiac muscle cells by the same channels (Lüttgau & Niedergerke, 1958), and it seems probable that in cardiac cell membrane acetylcholine does not affect this channel. Permeability to potassium is undoubtedly increased (Harris & Hutter, 1956; Rayner & Weatherall, 1959), and consequently hyperpolarization occurs as the membrane potential approximates more closely to the potassium equilibrium potential.

The action of acetylcholine on the heart is complicated by the effect seen

in isolated auricles which have failed to beat after cooling, prolonged activity (Bülbring & Burn, 1949) or inhibition by certain drugs such as proguanil ('Paludrine') and quinidine (Burn & Vane, 1949). In these circumstances addition of acetylcholine commonly stimulates the auricles to resume beating, and the same effect can be induced by vagal stimulation (Burn & Rand, 1957). Several explanations of these apparently excitatory actions have been put forward (Trautwein, 1963, p. 299, for review). They are observed particularly in conditions of potassium depletion or decreased potassium permeability: in either case it is likely that the increase of permeability produced by acetylcholine raises the membrane potential to a level at which activity is possible (Weidman, 1955a).

It is not known how acetylcholine alters the cell membrane so that its permeability to small cations is increased. Acetylcholine is itself a fairly small cation and as it is hydrolysed by a cholinesterase immediately below the cell membrane, its electrochemical potential gradient is directed strongly towards the cell interior. The length of the molecule, i.e. the occurrence of a chain of 5 atoms attached to the cationic head is fairly critical; alteration of the components of the chain has less effect on potency than altering its length (Alles & Knoefel, 1939; Ing, Kordik & Tudor Williams, 1952). The effect on the membrane of the motor end plate can 'be pictured as a formation of leaky ionic channels whose "protein lining" retains fixed negative charges and so rejects the passage of anions' (Katz, 1966, p. 126). In cardiac muscle, the opening by acetylcholine must be supposed to be more limited. As the hydrated potassium ion is smaller than the hydrated sodium ion, it is not difficult to visualize such a limit, but it also then becomes necessary to envisage a quite different channel by which sodium and calcium ions enter.

OTHER ONIUM COMPOUNDS

As far as evidence is available, other onium compounds act fundamentally on membranes in the same way as acetylcholine, but changes in chemical structure have two consequences which can greatly alter the final outcome. One consequence occurs if an ester linkage is not present, so that the compound is not rapidly hydrolysed by cholinesterase and so not quickly inactivated. The other consequence is that variation in structure considerably affects the affinity for particular tissues, so that relative specificity for one site or another is common. These two principles are sufficient to account for the properties of the monoquaternary carbachol (carbaminoylcholine), virtually identical in action with acetylcholine but not destroyed by cholinesterase and so persistent, and the bisquaternary suxamethonium (succinylcholine), preferentially active at motor end plates and hydrolysed relatively slowly and mainly by plasma cholinesterase (Fig. 1). Suxamethonium, like acetylcholine, depolarizes motor end plates by increasing their permeability to small cations. As it is removed more slowly, the increase persists for longer, and the muscle remains