

N_1 -aralkyl- N_2 -acyl hydrazines caused the appearance of powerful sedative, instead of anti-depressant activity.

35 Mode of Action of Antifibrillatory Drugs. E. M. VAUGHAN WILLIAMS and L. SZEKERES (United Kingdom).

Investigators still disagree how antifibrillatory drugs act. The problem is how they prolong the effective refractory period (minimum interval between stimuli for propagation of second action-potential) although they do not affect the absolute refractory period. Some still believe increased duration of action potentials responsible, others that antifibrillatory drugs slow down the recovery of mechanism by which depolarization is achieved.

To test these two hypotheses, measurements were made, on the same preparations of isolated rabbit atria, of: (a) highest frequency stimuli could be followed; (b) threshold current for producing fibrillatory responses; (c) conduction velocity; (d) contractions; and (e) intracellular potentials, during exposure to drugs of dissimilar structure, quinidine, procaine, procaine-amide, papaverine and dibenamine, from $5 \cdot 10^{-6}$ – 3×10^{-5} .

All drugs reduced maximum driving frequency and increased fibrillation threshold, dose-response curves being parallel. All reduced conduction velocity, but hardly affected contractions at the concentrations used. The time taken for repolarization to half the full resting potential was unchanged, a fact consistent with absence of change in absolute refractory period. The time for complete repolarization was either unchanged, or slightly prolonged at high doses to an extent insufficient to account for the great prolongation of effective refractory period. The resting potential was unchanged.

In contrast, the rate of rise of the action potential was greatly reduced by all drugs, implying that the property held in common was interference with the phase of depolarization. Such interference would necessitate a longer recovery period before the depolarization mechanism could be reactivated, and so would prolong the effective refractory period.

36 Competition between β -Haloalkylamines and Norepinephrine for Sites in Cardiac Muscle. R. F. FURCHGOTT and S. J. KIRPEKAR (U.S.A.).

Four β -haloalkylamines, N - α -naphthylmethyl- N -ethyl- β -bromoethylamine (SY28), N -cyclohexylmethyl- N -ethyl- β -chloroethylamine (GD31), phenoxybenzamine (PB), and Dibenamine (DB), have been studied on isolated, left atria of guinea pigs. These agents do not antagonize the cardiac stimulating effects of catecholamines, and therefore it is concluded that they do not react with cardiac β -receptors. However, they do produce certain effects, which are listed below along with postulated mechanisms of action: (1) Prolonged positive inotropic effect and depletion of endogenous norepinephrine (NE) in normal atria. Mechanism:

reaction with storage and binding sites for NE. Potency: SY28 > GD131 > PB > DB; (2) Transient positive inotropic effect on atria from reserpinized animals after "repletion" of such atria with NE, followed by irreversible blockade against further "repletion". Mechanism: reaction with binding sites for NE, probably on nerve terminals. Potency: SY28 > GD131 > PB > DB; (3) Marked irreversible potentiation of inotropic effect of added NE. Mechanism: reaction with sites with which NE combines in the process of its active removal or inactivation. Potency: PB > DB > GD131 > SY28.

All of these agents irreversibly block adrenergic α - (excitatory) receptors of smooth muscle (potency: SY28 > PB > DB > GD131). The sites with which they irreversibly compete with NE in heart may have some reactive grouping in common with smooth muscle α -receptor sites. However, the varying orders of potency associated with the different activities may indicate fundamental differences in the nature of the sites under consideration.

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37 Theophylline Structure as Related to Cardiac Inotropic Activity. H. F. HARDMAN (U.S.A.).

The relationship between changes in chemical structure and pharmacological activity is complex. Albert⁽¹⁾ emphasized the importance of drug ionization as a factor to be considered in such relationships.

The methylated xanthines such as theophylline and caffeine have measurable positive inotropic activity on cardiac tissue of several animal species. In the pH range of 6.5–8.5 theophylline ionizes as an anion (pK_a 8.6) whereas caffeine lacks an ionizable hydrogen and cannot exist in the anionic state. Both drugs exist primarily in the non-ionized state at pH 7.4 suggesting that their cardiac inotropic action may be related to this physical form of the drugs. Halogen substituted derivatives of theophylline which exist primarily in the anionic state at pH 7.4 lack positive inotropic activity.

The isolated perfused turtle heart (*Chrysemys picta*) was employed to evaluate the effect of drug ionization upon cardiac inotropic activity in a series of methylated xanthines having different ionization characteristics. This preparation was chosen because pH per se over the range of 6.5–8.5 does not affect the rate or amplitude of contraction of the preparation. This situation allows one to examine the relative effect of the ionized and nonionized form of the drug.

The conclusion reached was that cardiac positive inotropic activity in the methylated xanthines was directly related to the concentration of nonionized drug presented to the turtle heart. Confirmatory evidence was obtained in mammalian cardiac tissue within a more restricted pH range.

1. ALBERT A. (1954), *Pharm. Rev.*