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MECHANISM OF CARDIOVASCULAR ACTIONS OF HEPTANOLAMINES

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It has been suggested that heptaminol and methylheptaminol should be used as myocardial stimulants because they have cardiotonic actions similar to those of cardiac glycosides. However, as these aliphatic amines show definite sympathomimetic effects, the mechanism of their actions on the heart was investigated, in order to determine whether digitalis-like properties are involved in these effects. The pattern of pharmacological actions of heptaminol and methylheptaminol was compared with that of catechol amines, tyramine and k-strophanthin. The influence of atropine, hexamethonium, cocaine and reserpine was also investigated. The results show that both heptanolamines have a long-lasting cardiostimulant action which is abolished by cocaine and absent in reserpine pretreated animals. The pharmacological activity of these drugs may be entirely attributed to an indirect sympathomimetic action of the tyramine type, probably due to release of endogenous catechol amines. None of the experimental findings is consistent with the alleged digitalis-like action of these compounds.

Among the aliphatic amines, the heptylamines with an alcoholic function on carbon two have been the object of a more detailed pharmacological study, as they show cardiostimulating properties which are particularly intense and long-lasting. The two most active compounds of the series, heptaminol (6-amino-2-methyl-2-heptanol ; 2831 RP ; Heptamyl ; Cortensor) and methylheptaminol (6-methylamino-2-methyl-2-heptanol ; 3738 RP ; Aranthol), have been employed in the therapy of various clinical conditions including heart failure. Their use in heart failure is based on the experimental work of Loubatières (1949a & b, 1951) and Loubatières, Bouyard, Macabies & Mouralis (1949), who observed digitalis-like cardiotonic effects on the cat papillary muscle preparation fatigued by repeated electrical stimulation and on the dog ventricle *in situ*. Coraboeuf & Boistel (1953), recording the action potentials of cardiac tissue by means of intracellular microelectrodes, concluded that heptaminol shows powerful cardiotonic effects.

These heptanolamines, however, exhibit pharmacological actions which may be interpreted as depending on an activation of sympathetic receptors (Jackson, 1947 ; Walton, Belkin & Brodie, 1947 ; Huggins, Handley & La Forge, 1949 ; Walton & Brodie, 1949 ; Marsh & Herring, 1951 ; Garrett, 1954 ; v. Haxthausen, 1955 ; Hille & Teske, 1957). It thus seems necessary to characterize the nature of their cardiostimulating action, in order to ascertain whether, as well as their sympathomimetic action, there is also a digitalis-like component which may significantly contribute to the cardiac effects.

METHODS

Isolated atria of rabbit and guinea-pig. The atria were carefully dissected from the heart of animals killed by a blow on the neck and immediately bled; they were suspended in Tyrode solution at 29° C. This solution contained sodium chloride 8.0 g, potassium chloride 0.2 g, calcium chloride 0.2 g, sodium bicarbonate 1.0 g, sodium dihydrogen phosphate 0.5 g, dextrose 1.0 g per litre and was saturated with oxygen. The isolated organ bath had a capacity of 50 ml. The contractions were recorded on a smoked drum by a spring lever with a tension of 0.5 to 1.0 g (Greeff, Benfey & Bokelmann, 1959).

Cat blood pressure, nictitating membrane and electrocardiogram. Cats were anaesthetized with chloralose in a dose of 0.1 g/kg (10% solution in propylene glycol—Malafaya-Baptista, Simões & Osswald, 1954) by intraperitoneal injection. Carotid blood pressure was recorded with a mercury manometer. The right nictitating membrane was connected to a frontal writing lever with a tension of 1 to 2 g, magnifying the response 6 to 7 times. The electrocardiogram was recorded from leads D II, D III and aVR or aVL with a direct-writing apparatus. Observations were made on the effect of intravenous injection of heptanolamines and of the other drugs infused at the constant rate of 0.5 to 1.0 ml./min until the death of the animal.

Isolated rabbit ear. The ear was cut at the base immediately after the animal was killed, the central artery dissected and cannulated; perfusion was at constant pressure (20 to 40 cm water) with Tyrode solution at room temperature. The flow through the ear vessels was recorded with a "Palmer" drop-recording assembly. Injections were given in a constant volume (usually 0.2 ml.) by means of a special cannula provided with a small tap included in the perfusion circuit, immediately before the cannula.

Isolated seminal vesicles of guinea-pigs. The method was that of Malafaya-Baptista, Garrett & Osswald (1956), using Tyrode solution containing magnesium chloride (10 mg/l.).

Isolated rabbit intestine. The pendular contractions of a piece of jejunum from a freshly killed rabbit were registered with a frontal writing lever. Tyrode solution with magnesium chloride, oxygenated, at 37° C, was used.

Ballistocardiographic and electrocardiographic studies. Ultra-low frequency acceleration ballistocardiograms were obtained by adapting to the experimental animal (dog) the table described by Rappaport (1956a & b) and employing an electrochemical accelerator (Elliot, Packard & Kyrazis, 1954). This system when loaded with the weight of 10 kg (average weight of the animals used) presented the following characteristics: natural frequency, 0.14 to 0.17; dampening, 4 to 28%; weight of the platform, 2.4 kg. The ballistocardiogram and the three standard leads of the electrocardiogram were simultaneously recorded with an optical writing electrocardiograph ("Triplex Elema"). Carotid pressure was recorded with a mercury manometer. Anaesthesia was by intravenous sodium pentobarbitone 40 mg/kg (10 to 20 mg/kg only in reserpine pretreated animals). A fuller description of the method is given by Moreira (1960).

Manometric experiments. These were carried out according to the usual manometric method (Warburg instrument), using as a source of mono-amine oxidase the preparation of mitochondria of guinea-pig liver (Schneider, 1948); 1 ml. of the enzymatic suspension corresponded to 0.7 g of the liver (fresh weight). As substrate tyramine, heptaminol or methylheptaminol (0.2 ml.= 20 μ-mole) was used. The centre well contained 0.3 ml. N potassium hydroxide; in the main compartment of the flask there were 0.4 ml. of M/15 phosphate buffer *p*H 7.2, 1 ml. of enzymatic suspension, 0.2 ml. M/50 sodium cyanide and 0.2 ml. M/10 semicarbazide. In some experiments inhibition of the deaminative oxidation of tyramine by the heptanolamines was investigated.

Reserpine pretreatment of animals. 3 mg/kg of reserpine in 10 to 20% ascorbic acid was injected intramuscularly 24 hr before the beginning of an experiment.

Substances used. (−)Adrenaline and (−)noradrenaline (Hoechst); tyramine hydrochloride (Roche); heptaminol hydrochloride (Heptamyl, Delalande); methylheptaminol hydrochloride,

prepared from the base (Aranthol, Knoll Pharmaceutical Co.); cocaine hydrochloride (Bios); reserpine (Serpasil, Ciba); atropine sulphate B.P. (Oakland); strophanthin k-β (Kombetin, Boehringer); k-strophanthoside (Strophoside, Sandoz); pentobarbital sodium U.S.P.; α-chloralose (Roche); hexamethonium bromide (Light). The doses of adrenaline, noradrenaline and reserpine are given in terms of the bases; all other doses refer to the salts used.

RESULTS

Isolated atria of the guinea-pig. Both heptanolamines caused similar effects, namely, marked increase, proportional to the dose, of the amplitude and rate of contractions. These inotropic and chronotropic effects were sometimes preceded by a brief phase of cardiac inhibition, abolished by atropine (4×10^{-5}). Heptaminol and its methylated derivative are about 10^4 times less potent than noradrenaline, and their effects developed more slowly. Strophanthin k had no positive inotropic effect in concentrations up to 10^{-6}. The effects of heptanolamines were potentiated by hexamethonium. Cocaine (0.5 to 1×10^{-6}) reduced or abolished the effects of heptanolamines (Fig. 1). The concentration of cocaine greatly increased the response to noradrenaline and reduced or abolished the response to tyramine. On atria obtained from animals pretreated with reserpine, on which tyramine had no action, heptaminol and methylheptaminol did not produce any effect.

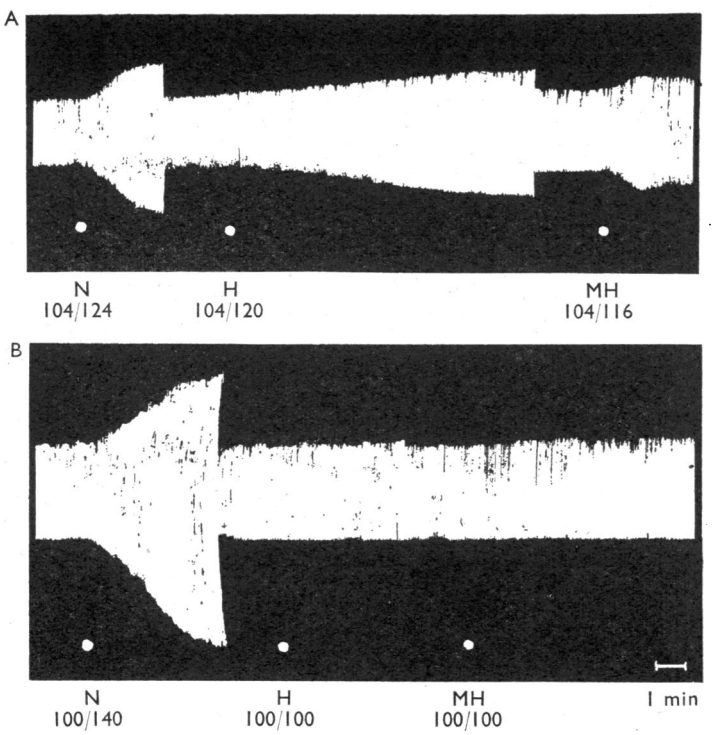

Fig. 1. Isolated guinea-pig atria. N=noradrenaline 10^{-8}; H=heptaminol 0.5×10^{-4}; MH=methylheptaminol 10^{-5}. Between the tracings A and B, 0.5×10^{-6} cocaine hydrochloride was kept in the bath. The numerals indicate the heart rate before and after the administration of each drug.

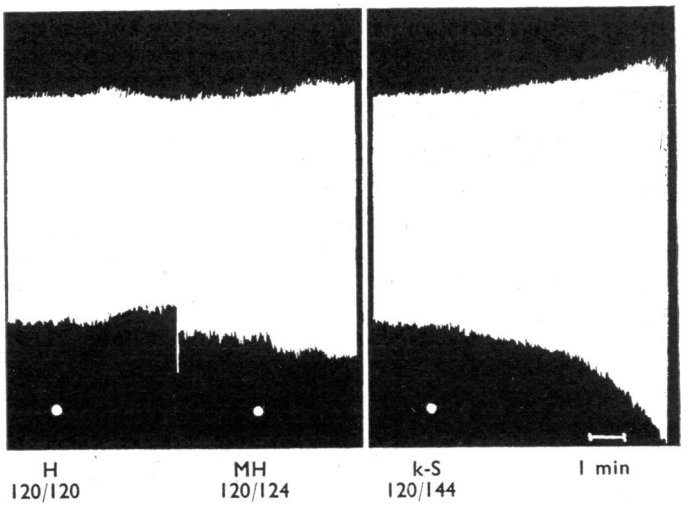

Fig. 2. Isolated rabbit atria. The animal was treated with reserpine 3 mg/kg injected intramuscularly 24 hr prior to the experiment. The numerals indicate heart rate. H=heptaminol 2×10^{-4}; MH=methylheptaminol 2×10^{-4}; k-S=strophanthin k 10^{-6}.

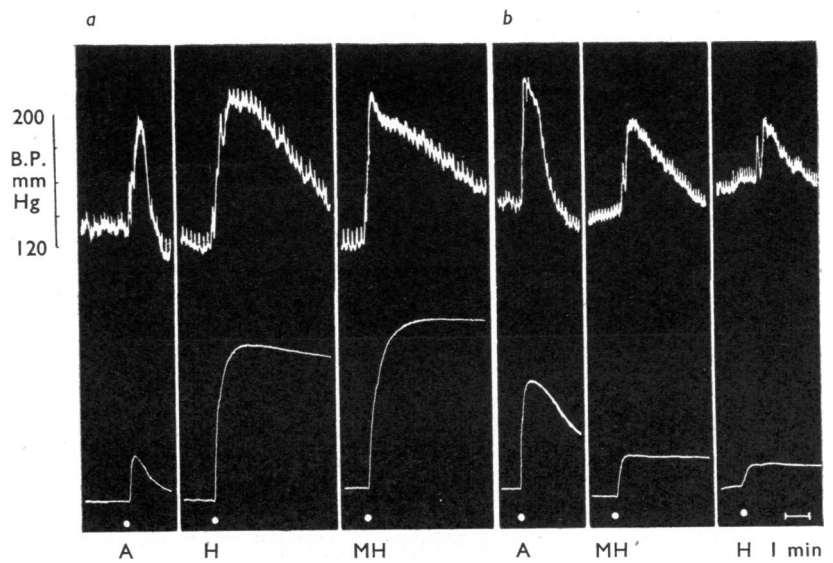

Fig. 3. Cat blood pressure and nictitating membrane contractions. Cat, female, 2.7 kg, chloralose injected intraperitoneally 0.1 g/kg. A=10 μg adrenaline; H=15 mg heptaminol; MH=15 mg methylheptaminol all injected intravenously. Between a and b, 5 mg/kg cocaine hydrochloride was injected intramuscularly.

Isolated atria of the rabbit. The cardiostimulating actions of the two heptanolamines were also modified by cocaine or by reserpine pretreatment in the same way as those of tyramine, as described above for the guinea-pig atria. Strophanthin k,

however, in this preparation had a powerful positive inotropic action, as a rule without an increase in rate. The response to strophanthin was not altered by cocaine and was present, without apparent change, even in reserpinized atria (Fig. 2).

Blood pressure and nictitating membrane of the cat. The blood pressure rises caused by the two heptanolamines were longer-lasting than that produced by equipressor doses of adrenaline or noradrenaline and quite comparable to that caused by tyramine. In order to obtain pressor effects of similar amplitude it was necessary to employ doses of heptanolamines respectively 2,000, 1,000 and 15 times greater than those of noradrenaline, adrenaline and tyramine. The nictitating membrane responded to heptanolamines with prolonged contractions, which were much larger than those produced by equipressor doses of adrenaline or tyramine. Hexamethonium (5 mg/kg) did not reduce the hypertensive effect of heptanolamines. The intramuscular injection of cocaine 5 mg/kg greatly enhanced the actions of adrenaline and noradrenaline, but markedly depressed or even abolished the responses of the blood pressure and nictitating membrane to tyramine and heptanolamines (Fig. 3). In cats pretreated with reserpine, adrenaline and noradrenaline exerted their usual effects while tyramine and heptanolamines were ineffective.

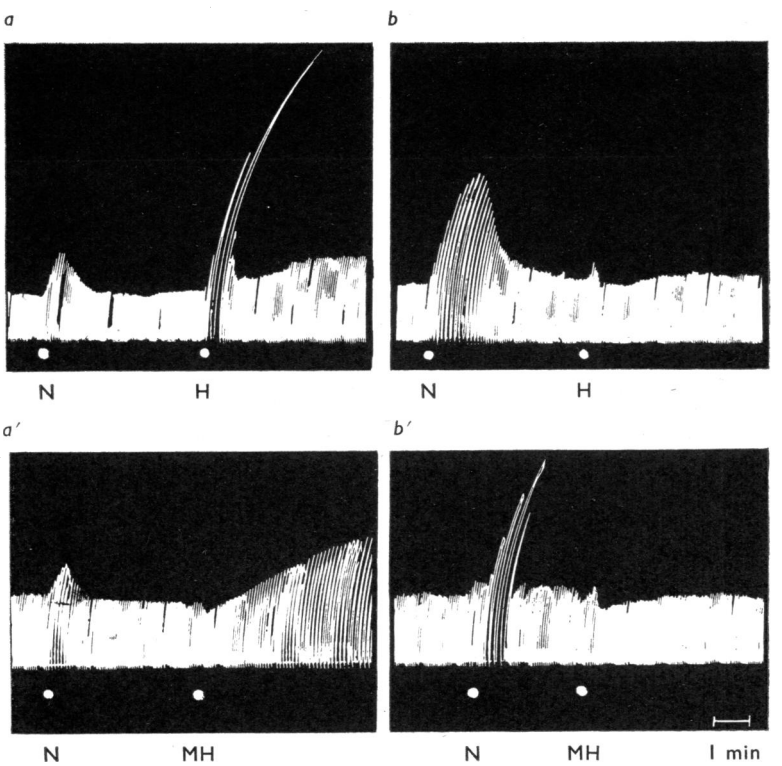

Fig. 4. Rabbit isolated ear. Recordings a and b were obtained from the same preparation, while recordings a′ and b′ were from another preparation. N=0.05 μg noradrenaline; H=25 mg. heptaminol; MH=12 mg methylheptaminol all injected intra-arterially. Between tracings a and b, and a′ and b′, there was an interval of 20 min during which perfusion was switched to Tyrode containing 2×10^{-6} cocaine hydrochloride.

Isolated rabbit ear. The sustained vasoconstriction which was observed after intra-arterial injection of high doses of the two heptanolamines was sometimes preceded by a brief increase of the flow. The vasoconstriction was reduced or abolished after perfusion with Tyrode solution containing cocaine 2×10^{-6}, which regularly produced potentiation of noradrenaline vasoconstriction (Fig. 4). In the ears obtained from reserpinized animals both heptanolamines were almost ineffective, while the vasoconstrictor activity of noradrenaline was unaffected.

Isolated seminal vesicles of guinea-pig. The effects of cocaine or of reserpine pretreatment on the activity of heptanolamines were also evident in these experiments. In normal preparations the heptanolamines are 200 to 500 times less effective than adrenaline or noradrenaline.

Isolated rabbit intestine. The relaxing effect of heptanolamines on this preparation was very slight, and it was necessary to use about 20,000 times the dose of noradrenaline to obtain comparable effects.

Cat electrocardiogram. During the infusion of heptanolamines the following phenomena were observed (Fig. 5). There was an almost immediate rise of blood pressure, which remained high for a time and then returned to the normal values to fall abruptly in the terminal phase, marked and prolonged contraction of the nictitating membrane, maximal mydriasis and salivation. In the terminal phase

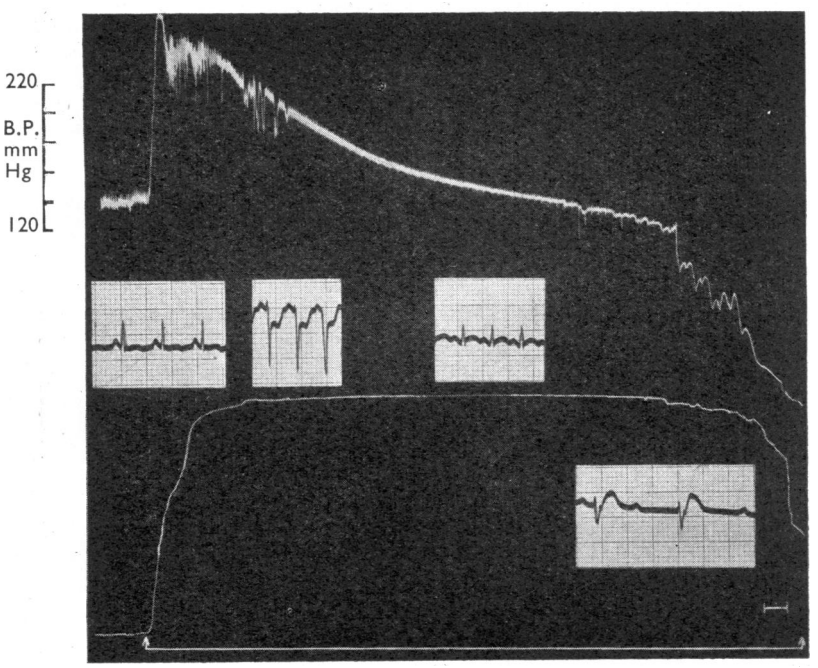

Fig. 5. Cat blood pressure, nictitating membrane contractions and ECG (lead D II). Cat, female, 3 kg, anaesthetized with chloralose 0.1 g/kg injected intraperitoneally. Between the arrows—slow intravenous infusion, at constant speed (1 ml./min), of a 3% methylheptaminol solution.

pulmonary oedema, confirmed at necropsy, was always present. Electrocardiographic records showed marked tachycardia, with a disturbance of the intraventricular conduction (bundle branch block) which disappeared as a rule spontaneously in the course of the experiment. Sinus rhythm remained until in an advanced phase of the intoxication there was failure of the auriculo-ventricular conduction and low-voltage complexes appeared. Very often an increase in the amplitude of the P-wave was observed. Strophanthin k, also infused intravenously, had quite different effects on the blood pressure (which remained unchanged up to the final phase) and on the nictitating membrane (no contraction). The usual pattern of electrocardiographic effects of digitalis was observed.

Ballistocardiographic and electrocardiographic studies. During the blood pressure rise caused by the injection of 2 to 3 μg/kg of adrenaline a very accentuated increase in the amplitude of the H, I and J waves of the ballistocardiogram was observed. Simultaneously, bradycardia and the following electrocardiographic changes were recorded: the T-wave became negative in D I and positive in D II and D III.

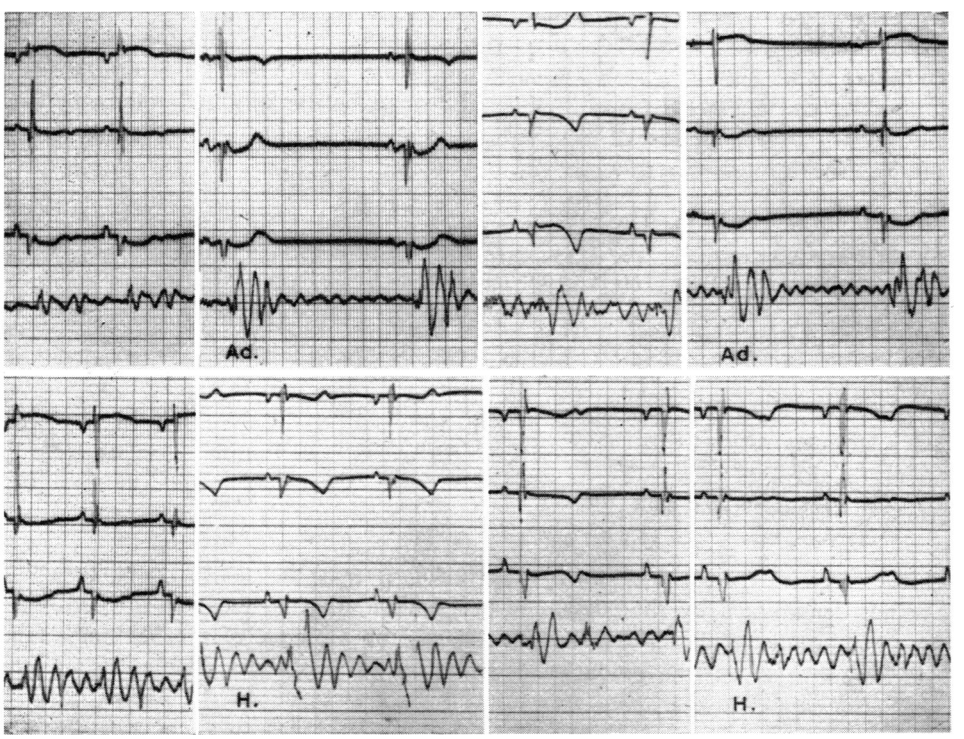

Fig. 6. Dog electrocardiogram (leads D I, D II and D III) and ultra-low frequency ballistocardiogram. Between the second and the third tracings, and the sixth and the seventh tracings, 5 mg/kg cocaine hydrochloride was injected intramuscularly; the upper and lower tracings were taken from different animals (top: dog, male, 10 kg; lower: dog, male, 9 kg; anaesthetized with sodium pentobarbitone 40 mg/kg injected intravenously). Ad=20 μg adrenaline injected intravenously; H=5 mg/kg heptaminol injected intravenously.

The modifications of the ballistocardiogram provoked by the injection of 5 to 7 mg/kg of heptaminol and of 4 to 6 mg/kg of methylheptaminol were similar, but more prolonged. In the electrocardiographic tracings changes of the T-wave like those already described for adrenaline were recorded. The heart rate increased moderately, at times after an initial and transient decrease. Cocaine (5 mg/kg injected intramuscularly) affected the response to adrenaline and to heptanolamines in a different way. Thus, the effects of adrenaline on the ballistocardiogram and the electrocardiogram were not significantly altered, but the effects of the heptanolamines were reduced or even abolished by cocaine (Fig. 6). The pressor effects of adrenaline were reinforced by cocaine, while the blood pressure responses to the heptanolamines were markedly reduced or abolished. In animals pretreated with reserpine, adrenaline still had its typical effects, but the heptanolamines were almost ineffective, even in doses of 7 to 20 mg/kg. The pressor effect of adrenaline was clearly potentiated after reserpine treatment, but the pressor effect of methylheptaminol was abolished. In some experiments heptaminol produced a biphasic response with an initial, small and brief, hypertensive spike, followed by a long-lasting hypotension. A reduction in the amplitude of the H, I and J waves of the ballistocardiogram, followed by a transient increase, was concomitantly recorded. In dogs rendered deeply hypotensive by reserpine diastolic waves of a considerable amplitude were recorded in the ballistocardiogram. k-Strophanthoside (30 μg/kg) did not produce any significant changes in the amplitude of the ballistocardiogram over a period of observation of about 30 min, and no alterations of the electrocardiogram were recorded.

TABLE 1

MEAN VALUES OF OXYGEN UPTAKE (μl.) WITH GUINEA-PIG LIVER MITOCHONDRIA SUSPENSION

	Time in min		
Flasks containing	10	30	60
Amine oxidase + tyramine 20 μ-mole	54	122	182
Amine oxidase + heptaminol 20 μ-mole	0	3	6
Amine oxidase + tyramine 20 μ-mole + heptaminol 20 μ-mole	54	123	183
Amine oxidase	4	5	5
Heptaminol 20 μ-mole	0	0	0

Manometric experiments. These experiments showed that the two heptanolamines are not deaminated by the enzymatic preparation, that is, they are not substrates for mono-amine oxidase. On the other hand, the presence of the heptanolamines had no influence on the oxidative deamination of tyramine. Table 1 shows the results of a typical experiment.

DISCUSSION

The results obtained show that heptaminol and methylheptaminol have similar pharmacological properties, which appear to depend on an activation of adrenergic receptors. The potency of heptanolamines in relation to that of adrenaline or noradrenaline varied within wide limits, but qualitatively there were no differences

between the effects of heptanolamines and of catechol amines in any of the tests used. Heptaminol and methylheptaminol produced an increase in the cardiac contractions, tachycardia, hypertension, constriction of isolated vascular beds, contraction of the nictitating membrane, mydriasis, inhibition of intestinal motility and contraction of the seminal vesicles. A close similarity in the effects on the electrocardiogram was also evident. After the injection of adrenaline or of heptanolamines bradycardia of vagal origin, depression of the ST-segment and increase in amplitude of the P-wave were prominent. The effect of heptanolamines in increasing the H, I and J waves of the ballistocardiogram is similar to the effect observed after the injection of catechol amines, which was described by Darby, Goldberg, Gazes & Arbeit (1957), Hoitink & Knoop (1957) and Moreira (1960). An increase in the amplitude of these ballistocardiogram waves is attributed to an increase in the force of systolic contraction or a decrease in peripheral resistance. It seems probable that the effect of heptanolamines on the ballistocardiogram is due to their cardiotonic action.

The results obtained after cocaine lead to the conclusion that the inotropic effects of adrenaline are influenced in a different way from those produced by heptanolamines. Indeed, while adrenaline retains its cardiostimulating effect, the actions of heptanolamines on the ballistocardiogram and the electrocardiogram are clearly antagonized. A similar observation was made in dogs pretreated with reserpine, in which clear-cut effects of adrenaline on the ballistocardiogram and the electrocardiogram were observed, while heptanolamines produced only insignificant effects. It is interesting that during the hypotension caused in some of these dogs by heptaminol there was only a small and brief increase of the ballistocardiographic amplitude ; this is a remarkable finding, since hypotensive drugs which lessen the peripheral resistance cause a considerable increase in the amplitude of the ballistocardiogram during the whole period of hypotension.

The comparative study of the effects of heptanolamines and catechol amines, on one hand, and strophanthin, on the other hand, on different pharmacological tests (acute lethal intoxication of the cat, dog ballistocardiogram and electrocardiogram, rabbit and guinea-pig atria) shows that heptanolamines have no digitalis-like action. On the guinea-pig isolated atria strophanthin was ineffective while heptanolamines had a marked cardiostimulating action ; furthermore, on the rabbit atria both strophanthin and the aliphatic amines produced positive inotropic effects, but pretreatment of the test animal with reserpine or cocainization of the atria abolished the cardiac response to heptanolamines, without modifying the effects of strophanthin.

The electrocardiographic modifications provoked by slow infusion of heptanolamines or of strophanthin were also distinct: the amines induced a typical pattern of adrenergic cardiac activation without deterioration of the electrocardiographic tracings up to the final phase, while strophanthin poisoning led to early and typical digitalis effects on the electrocardiogram. On the electrocardiogram and ballistocardiogram of the dog heptanolamines had clear effects, while strophanthin was without any action.

Loubatières (1949b, 1951) suggested an identical mechanism of action for digitalis and heptaminol. The similarity, stressed by him, between the inotropic effects of

the two types of drugs on the isolated papillary muscle and on the right ventricular fibres does not allow such a far-reaching conclusion; indeed a more detailed pharmacological analysis leads us to reject this concept. Cairoli, Reilly & Roberts (1961) attribute the effects of digitalis to the release of catechol amines in the cardiac tissues, because reserpine pretreatment produced a reduction of 30% in the effect of ouabain on the isolated papillary muscle of the cat. In our experience, atria from rabbits pretreated with reserpine, which did not respond to tyramine, were sensitive to the concentrations of strophanthin usually used; furthermore, cocainization abolished the effects of tyramine but had no influence on the action of strophanthin. The cardiac effects of catechol amines are antagonized by dichloroisoproterenol, a drug which, however, does not affect the response of the heart to digitalis (Moran & Perkins, 1958). The hypothesis that digitalis has an indirect adrenergic action is not in accordance with its known biochemical effects on the myocardium (Mayer & Moran, 1960).

Regarding the type of sympathomimetic action of heptanolamines, a stimulation of sympathetic ganglionic structures may be ruled out since the effects of heptanolamines are not affected by hexamethonium. Heptanolamines are not a substrate of mono-amine oxidase nor do they inhibit this enzyme, and this fact makes it possible to exclude enzymatic inhibition as part of the effects of these substances. It is known (Fleckenstein & Bass, 1953; Fleckenstein & Burn, 1953; Fleckenstein & Stöckle, 1955) that the actions of some aromatic amines like tyramine are antagonized by cocaine and denervation. Later work (Carlsson, Rosengren, Bertler & Nilsson, 1957; Burn & Rand, 1958; Holtz, Osswald & Stock, 1960) showed that treatment with reserpine induces modifications in the activity of these amines which duplicate those occurring after cocaine or denervation. Our results show that heptanolamines behave like tyramine and should be included in this group. The action of these "indirect" amines would depend on the release of adrenaline and noradrenaline from tissue stores as has been suggested for the case of tyramine by Burn & Rand (1958) and demonstrated to occur under certain circumstances (Schümann & Weigmann, 1960; Schümann & Philippu, 1961; Burn & Burn, 1961; Lindmar & Muscholl, 1961). Further support for this interpretation of the actions of heptanolamines is the gradual onset and long duration of the effects of these amines.

The indirect mechanism of the sympathomimetic action of these compounds would satisfactorily explain the fact that drugs with structures as dissimilar as catechol amines and aliphatic amines should produce very similar effects, a fact that otherwise would hardly agree with the generally accepted notion of the existence of specific receptors for the adrenergic mediators.

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