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EFFECT OF FATTY ACIDS ON THE VENTRICULAR ARRHYTHMIA THRESHOLD IN THE ISOLATED HEART OF THE RABBIT

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1 The ventricular arrhythmia threshold (VAT) was measured in the isolated Ringer-perfused rabbit heart (Langendorff preparation) by applying a single 10 ms square-wave pulse of current to the left ventricle during the vulnerable period of late systole under normoxic and hypoxic conditions.

2 The sodium salt of the fatty acid was bound to albumen and incorporated in the Krebs-Henseleit solution which was maintained at 37°C and gassed with 95% O_2 and 5% CO_2 (normoxia) or 5% CO_2 in air (hypoxia).

3 Saturated fatty acids failed to alter the VAT under normoxia.

4 Naturally occurring long-chained saturated and mono-unsaturated fatty acids with chain lengths varying from 14 to 20 carbons, but not the 12 carbon lauric acid, potentiated the effect of the hypoxia in lowering the VAT.

5 Short-chained 8 and 10 carbon saturated and long-chained polyunsaturated fatty acids antagonized the effect of hypoxia on the VAT.

6 In addition the polyunsaturated acids antagonized the potentiating effect of the long-chained saturated and mono-unsaturated acids on the hypoxia in lowering the VAT.

7 The fatty acids did not alter the duration or type of the induced arrhythmia.

Introduction

A relationship proposed between the level of free fatty acids and cardiac arrhythmias is still controversial. Oliver and coworkers (Oliver, Kurien & Greenwood, 1968; Oliver & Kurien, 1969; Kurien & Oliver, 1970a) have claimed that a raised blood level of free fatty acids after acute myocardial infarction predisposes to cardiac arrhythmias but Rutenberg, Pamintuan & Soloff (1969), Gupta, Young, Jewitt, Hartog & Opie (1969), Nelson (1970), Hagenfeldt & Wester (1973) and Sharma (1977) have disputed this. Soloff (1970) produced ECG changes and arrhythmias in normal anaesthetized dogs when he infused a suspension of a long-chained saturated fatty acid intravenously and Misra, Stanley & Kezdi (1971) induced similar changes, and in addition cardiac dilatation with almost complete loss of contractility accompanied by death, in anaesthetized coronary artery-ligated dogs. Kurien and coworkers (Kurien & Oliver, 1970b; Kurien, Yates & Oliver, 1971) produced ventricular arrhythmias in anaesthetized coronary artery-ligated dogs by elevation of the blood free fatty acids with heparin, with or without intralipid. However, using similar techniques Opie and coworkers (Opie, Norris, Holland, Owen & Thomas, 1971; Opie, Norris, Thomas, Holland, Owen & Van Noorden, 1971) and Mbuyamba (1976) could not confirm that the arrhythmias induced were due to the raised free fatty acids in the blood.

Kostis, Mavrogeorgis, Horstmann & Gotzoyannis (1973) failed to demonstrate that elevation of the blood free fatty acids altered the ventricular fibrillation threshold in normal and coronary artery-ligated dogs but Wasilewska-Dziubińska (1975) and Borborola, Papp & Szekeres (1976) showed that fatty acids produced changes in heart muscle compatible with an arrhythmia inducing effect.

In the present study the ventricular arrhythmia threshold (VAT) was used as a measure of vulnerability to an induced cardiac arrhythmia. The effect of the sodium salt of the fatty acid, bound to albumen, on this parameter was studied in the isolated Ringer-perfused heart of the rabbit (Langendorff preparation) under normoxic and hypoxic conditions. The results demonstrate that (a) long-chained saturated fatty acids do not affect the VAT under normoxia but potentiate the lowering effect of hypoxia on the VAT and (b) this latter effect is antagonized by polyunsaturated fatty acids.

Methods

Ventricular fibrillation or a rapid tachycardia was induced in rabbit hearts perfused via the aorta with a

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modified Krebs-Henseleit solution (NaCl 120, $NaHCO_3$ 25, KCl 5.6, $CaCl_2$ 2.5, NaH_2PO_4 1.2, $MgSO_4$ 1.2, Na pyruvate 2.0 and glucose 11 mM) at 37°C by the method described previously (MacConaill & Murnaghan, 1967) with some modifications. The recording platinum wire hook electrodes were attached horizontally, one to the left and the other to the right ventricular wall; the ventricular action currents picked up as the potential difference between them was amplified and displayed on the upper beam of a dual beam oscilloscope. The upstroke of the R deflection was used to trigger the sweep of the scope in synchrony with the heart beat. An output pulse from the oscilloscope, synchronous with the start of the sweep and thus with the R wave of the electrogram, was passed through a scale of two counter; on the start of every eighth sweep the output of the counter triggered a Grass Model S44 Stimulator. After a set delay a 10 ms pulse was generated and applied via a constant current unit to the left ventricle via stainless steel clip electrodes, one being attached to the base and the other to the apex (cathode).

The ventricular arrhythmia threshold (VAT) was determined by measuring the minimal strength of current required to produce fibrillation or a rapid tachycardia when applied as a single pulse of current during the vulnerable period of late systole. Measurement of the width of the vulnerable period in a few trials indicated that it varied between 10 and 20 ms. Consequently the pulse was applied at 10 (and on occasions when in doubt at 5) ms steps during the latter half of the R-T interval. The minimal time after the R wave of the electrogram at which the 10 ms pulse had to be applied to induce the arrhythmia was called the vulnerable time. The minimal acceptable duration of the arrhythmia was set at 4 s because of difficulty in differentiating from groups of multiple extrasystoles which were commonly produced at the same or slightly lower level of current strength. The type of arrhythmia induced, monitored on a large oscilloscope screen (Airmec), was recorded as fibrillation or tachycardia. The duration of the arrhythmia was listed as persistent (>60 s) or nonpersistent. If a normal rhythm had not returned after 60 s, defibrillation was effected by manually infusing 0.5 M KCl (usually 0.5 ml sufficed) into the aortic cannula. In order to indicate the magnitude of change produced by the treatment on the VAT, despite the variation in magnitude of the latter among hearts, the VAT change ratio was calculated, i.e. VAT during treatment/VAT of the immediately preceding controls. All hearts were beating spontaneously. Hearts driven at a constant rate above the spontaneous rate via the atria could not be used because of the development of A-V block during exposure to hypoxia. Furthermore, driving the heart via electrodes attached to the right ventricle caused a lowering of the VAT.

The perfusion apparatus consisted of three heat-exchange glass columns connected to a perspex block fitted with a tap so that the fluid from any one column could be selected. Each column was fed from a reservoir bottle; the control perfusion fluid was gassed with 5% CO_2 in O_2. In order to expose the heart to hypoxia the perfusion fluid was gassed with 5% CO_2 in air ($\approx 20\%$ O_2); anoxia was induced by gassing with 5% CO_2 in nitrogen. The perfusion pressure was equivalent to 54 cm of solution. At the front of the perspex block an opening, with tap, permitted the injection of KCl into the perfusion solution just above the aortic cannula; at the back of the block was an opening with tap for the removal of air bubbles from the cannula when required. The temperature of the perfusion fluid was monitored by a thermistor probe inserted into the right ventricle via the cut pulmonary artery.

The sodium salt of the fatty acid, unless otherwise stated, was bound to albumen before adding to the modified Krebs-Henseleit solution. The albumen (Bovine fraction V, Sigma) was defatted as described by Chen (1967). It was dissolved in water, mixed with activated charcoal, brought to pH 3 and stirred for one hour over an ice-bath, centrifuged initially at 4,000 *g* for 15 min and the supernatant again at 26,000 *g* for 30 min. It was dialysed for 24 h against distilled water at 10°C. The hot solution of the sodium salt of the fatty acid was added during continuous stirring to the albumen solution maintained at 35–39°C. The albumen-fatty acid mixture was incorporated in the modified Krebs-Henseleit solution to give a final concentration of 0.15 mM albumen. Perfusion with solutions deficient in O_2 was rarely maintained for a period longer than 5 min in order to avoid undue depression of the heart. If the VAT had not been determined by the end of this hypoxic period the heart was perfused with oxygenated fluid before testing again with an O_2-deficient solution.

Results

A half hour after starting the perfusion the heart rate was approximately 185 beats/min, the force 30 g and the coronary flow 22 ml/min. At the end of the 5 h experiment the three parameters had decreased by 28%, 80% and 62% respectively. During exposure to the combination of hypoxia and the fatty acid the average heart rate was initially 138.2 ± 2.67 and decreased 14.0 ± 1.45 beats/min. However, there was no significant difference in the change in rate between the hearts where the fatty acid potentiated the effect of hypoxia on the VAT and those where it did not.

Ventricular arrhythmia threshold (VAT)

The currents required to induce arrhythmia in most trials varied between 3.2 and 16 mA in the controls. The control values either remained constant or varied throughout the experiment; in the latter case the test values followed a similar pattern but at a different current level when altered by the treatment. Repeated trials were carried out on each heart, each being preceded by its own control values and only one fatty acid (or combination) was tested on each heart.

Under normoxic conditions when 4–8 mM caproic acid or 2–4 mM caprylic acid or its salt, sodium octanoate, were dissolved in the Krebs-Henseleit solution they failed to alter the VAT significantly (see Table 1). Because of its insolubility, 0.6–0.9 mM sodium palmitate was bound to 0.15 mM albumen incorporated in the Krebs-Henseleit solution. Its VAT change ratio did not differ significantly from unity. Albumen (0.15 mM) alone did not alter the VAT.

To try to simulate the conditions of the heart muscle during infarction, the Krebs-Henseleit solution was gassed with a mixture of 5% CO_2 in air ($\approx$20% O_2) instead of in O_2 because apart from other changes, recently infarcted tissue is hypoxic. This method was selected as a model because of its simplicity although it is realized that the 'global' hypoxia in these experiments differs from that of localized ischaemia during infarction, i.e. acidosis, K cell loss, etc, and consequently any comparisons must be considered with reservations. The combined effect of this hypoxic environment with the sodium salt of the fatty acid bound to albumen was investigated. Table 2 shows the results with 11 naturally occurring fatty acids with chain lengths varying from 8 to 20 carbon atoms and with zero to 4 double bonds. The concentrations of sodium octanoate and caprate listed in the table are much larger than that of the sodium salts of the other fatty acids. The latter could not be tested at higher concentrations without precipitation. Hypoxia alone significantly lowered the VAT from the control normoxia as did also all the fatty acid salts combined with it except octanoate, caprate, laurate, linoleate, linolenate and arachidonate. Sodium octanoate and caprate and the polyunsaturated linoleate, linolenate and arachidonate significantly antagonized the lowering effect of hypoxia, laurate had no effect while the sodium salt of the saturated fatty acids, myristic, palmitic, stearic, arachidic, and of the mono-unsaturated oleic acid significantly potentiated the lowering effect of hypoxia on the VAT. However, when 0.15 mM stearate was combined with anoxia, which lowers the VAT more than hypoxia, it failed to potentiate the effect of anoxia. There was no indication that the VAT changes induced by hypoxia were exacerbated with repeated testing.

With the exception of octanoate and caprate the FFA/albumen ratio varied between 1 to 4.

Of considerable interest is the fact that the three polyunsaturated fatty acids, unlike the saturated or mono-unsaturated, did not potentiate the lowering effect of hypoxia on the VAT but significantly antagonized it.

The question that presented itself was – if polyunsaturated fatty acids antagonize the effect of hypoxia would they also antagonize the effect of the fatty acids which potentiate the lowering effect of hypoxia on the VAT? When linoleate was combined with oleate so that it constituted 25 to 50% of the mixture it not only significantly antagonized the potentiating effect of the oleate ($P<0.001$) but also the effect of the hypoxia itself ($P<0.01$); when it constituted only 10% of the mixture it significantly ($P<0.01$) antagonized the effect of the former but not of the latter (Table 3). Similarly 20% linolenate not only significantly antagonized the potentiating effect of palmitate ($P<0.001$) but also the effect of hypoxia ($P<0.001$); 10% linolenate significantly ($P<0.001$) antagonized the effect of the former but not of the latter.

When a mixture of the sodium salt of saturated and unsaturated acids in the proportion present in 'normal' plasma (palmitoleic 0.02, myristic 0.01, palmitic 0.05, stearic 0.03, oleic 0.05, linoleic 0.03, linolenic 0.004 and arachidonic acids 0.006 mM; Geigy Scientific Tables), where the polyunsaturated acid constituted 20% of the mixture, were combined with

Table 1 Effect of fatty acids on the ventricular arrhythmia threshold (VAT) change ratio during normoxia in rabbit isolated heart

Treatment	*Concentration* (mM)	*Number of hearts*	*trials*	*VAT change ratio* Mean ± s.e.mean
Caproic acid	2–8	1	6	1.05 ± 0.06
Caprylic acid	2–4	2	11	1.26 ± 0.18
Sodium octanoate	2–4	3	10	0.96 ± 0.09
Sodium palmitate + albumen	0.6	4	16	0.96 ± 0.06

Table 2 Effect of saturated and unsaturated fatty acids on the ventricular arrhythmia threshold (VAT) change ratio during hypoxia in rabbit isolated heart

Treatment		*Concentration* (mM)	*Number of hearts*	*trials*	*VAT change ratio* Mean ± s.e.mean
Hypoxia		–	15	34	0.73 ± 0.03
Sodium octanoate	(8C:0)	2.0	4	12	0.93 ± 0.12**
Sodium caprate	(10C:0)	2.0	1	9	0.89 ± 0.08**
Sodium laurate	(12C:0)	0.6	2	12	0.85 ± 0.08
Sodium myristate	(14C:0)	0.6	2	16	0.54 ± 0.07***
Sodium palmitate	(16C:0)	0.6	4	20	0.63 ± 0.05**
Sodium stearate	(18C:0)	0.1	2	12	0.58 ± 0.04***
Sodium arachidate	(20C:0)	0.2	3	21	0.57 ± 0.04†
Sodium oleate	(18C:1)	0.2	2	16	0.43 ± 0.03†
Sodium linoleate	(18C:2)	0.3	2	17	0.89 ± 0.08**
Sodium linolenate	(18C:3)	0.3	3	16	0.83 ± 0.05*
Sodium arachidonate	(20C:4)	0.2	1	6	1.04 ± 0.03†

Significance of differences from hypoxia alone: * $P<0.05$; ** $P<0.02$; *** $P<0.01$; † $P<0.001$.

hypoxia the VAT change ratio in 15 trials was 0.72 ± 0.05 which was significantly different from unity but not from the effect of hypoxia alone.

Duration and type of arrhythmia

Hypoxia alone significantly increased the proportion of the induced arrhythmias that were persistent ($P<0.001$) and caused fibrillation rather than tachycardia ($P<0.05$) when compared with the normoxic controls. No significant clear cut pattern emerged in regard to the effect of the fatty acids on the duration or type of arrhythmia.

Vulnerable time

The control vulnerable time in 725 estimations was 82.1 ± 0.66 ms. Neither hypoxia alone nor combined with the fatty acid significantly altered the vulnerable time when compared with its normoxic controls with the single exception of sodium oleate which significantly ($P<0.01$) shortened it. This finding was unexpected in so far as the action potential duration of cardiac muscle is shortened by hypoxia. Two factors may have militated against a change: (a) during the period of hypoxia the R-T interval often lengthened initially, which was not necessarily associated with a decrease in heart rate, before it shortened and (b) the duration of the exposure to hypoxia at which the arrhythmia was induced varied from 1 to 5 min which depended upon how close to the threshold value one started testing.

Discussion

The results on the rabbit isolated Ringer-perfused heart have shown that (a) saturated fatty acids failed to alter the ventricular arrhythmia threshold (VAT) in a normoxic environment, (b) long-chained saturated and mono-unsaturated fatty acids with chain lengths varying from 14 to 20 carbons potentiated the effect of the hypoxia in lowering the VAT, (c) short-chained 8 and 10 carbon saturated acids and long-chained polyunsaturated acids antagonized the effect of hypoxia on the VAT, (d) the 12 carbon lauric acid, lying between the short- and long-chained saturated fatty acids, had no effect and (e) polyunsaturated

Table 3 Antagonism of saturated by polyunsaturated fatty acid on ventricular arrhythmia threshold (VAT) change ratio during hypoxia

Treatment	*Percentage polyunsaturated*	*Number of hearts*	*trials*	*VAT change ratio* Mean ± s.e.mean
Na oleate 0.2 mM + Na linolenate 0.2 mM	50	1	8	1.13 ± 0.10†
Na oleate 0.3 mM + Na linolenate 0.1 mM	25	1	8	0.96 ± 0.10***
Na oleate 0.18 mM + Na linolenate 0.02 mM	10	1	7	0.76 ± 0.05
Na palmitate 0.16 mM + Na linoleate 0.04 mM	20	2	8	0.94 ± 0.03†
Na palmitate 0.18 mM + Na linoleate 0.02 mM	10	2	16	0.77 ± 0.03

Significance of difference from hypoxia alone: *** $P<0.01$; † $P<0.001$.

acids not only antagonized the effect of hypoxia on the VAT but also the potentiating effect of the long-chained saturated and mono-unsaturated acid on hypoxia.

While a long-chained fatty acid significantly potentiated the effect of hypoxia, it failed to potentiate the effect of anoxia. Since a high concentration of free fatty acids (FFA) cause an increased demand for oxygen (Mjøs, 1971; Kjekshus & Mjøs, 1972) they would be expected to increase the degree of hypoxia so that it would approach that of the anoxic state. Since anoxia is more arrhythmogenic than hypoxia in so far as it lowers the VAT more (Murnaghan, 1975), then FFA when combined with hypoxia would be expected to increase the incidence of an arrhythmia.

One of the effects of hypoxia is that it shortens the action potential duration (APD) of cardiac muscle (Trautwein, Gottstein & Dudel, 1954). Cowan & Vaughan Williams (1977) showed that palmitate when bound to albumen in the Ringer solution potentiated the effect of hypoxia in shortening the APD but could not further shorten that produced by anoxia in guinea-pig ventricular muscle. Similar results have been obtained in this laboratory with rat isolated ventricular muscle (Corish, unpublished observations). Since a shortening of the APD is considered to be arrhythmogenic, this finding substantiates the demonstrated arrhythmogenic effect of palmitate during hypoxia when measured by the lowering effect on the VAT.

Kurien & Oliver (1970a) believe that an increase in FFA in excess of the primary albumen binding sites causes an increased intracellular level of FFA leading to an increased triglyceride synthesis, necessitating an increased oxygen usage and that the increased intracellular level of FFA exerts a detergent effect on the cell membrane, resulting in cation loss with the possible development of ectopic sites. Liedtke, Nellis & Neely (1978) have shown that increased serum FFA raises the tissue level of long-chain acylcoenzyme A esters and acylcarnitine levels. Shug & Shrago (1973) believe that long-chain acylcoenzyme A esters can inhibit adenine nucleotide translocation in heart mitochondria and that this inhibition can be reduced by free carnitine. These effects result in lowered subsarcolemmal cytosolic ATP levels and ATP is necessary for the maintenance of the plateau and APD. As glycolytic ATP is important for the maintenance of the APD (Opie, Nathan & Lubbe, 1979) the inhibition of glycolysis by increased intracellular FFA could account for the potentiating effect of palmitate during hypoxia.

While the above mentioned changes could account for the potentiating of the effect of hypoxia by long-chained saturated fatty acids, an explanation of the protective effect of the polyunsaturated fatty acids remains equivocal. Possibly their demand for oxygen would be less but this could hardly account for their antagonistic action. Of interest is the finding that long-chained saturated fatty acids when infused intravenously into dogs caused massive thrombosis and death but short-chained acids of 12 carbons and less and long-chained unsaturated acids did not do so (Connor, Hoak & Warner, 1963). Furthermore Mest, Blass & Forster (1977) have shown that arachidonic and linoleic but not linolenic acid protected against the arrhythmogenic action of $BaCl_2$ in rabbits and of ouabain in cats and guinea-pigs.

Shrade, Böhle, Biegler, Teicke & Ullrich (1960) measured the relative proportion of saturated to polyunsaturated FFA in serum of normal and diseased persons. In 16 healthy normal subjects 18–41 years of age, 19% of the FFA were polyunsaturated; in atherosclerotic patients with normal lipidaemia, 17% were polyunsaturated and in those with hyperlipidaemia 15% were polyunsaturated. After a myocardial infarction the oleic acid level of the FFA fraction in plasma was found to be increased (Jurand & Oliver, 1970); in addition, in the plasma lipid fraction a decrease in the percentage of linolenic acid was found by some workers (Bang, Mess Thaysen & Thygesen, 1968) or a decrease in the percentage of linoleic acid balanced by an increase in some saturated and mono-unsaturated fatty acids (Kirkeby, Myermann & Bjeikedal, 1968).

These results and those in the present study suggest that apart from an increased level of saturated free fatty acids, the relative proportion of saturated to polyunsaturated acids may play a significant role in determining the incidence of cardiac arrhythmias. However, a note of uncertainty may be introduced by the findings of Logan, Larking & Nye (1977) who found that when young rats were fed a diet rich in linoleic acid, the sensitivity to ventricular fibrillation induced by intravenous $CaCl_2$ was not decreased when compared to control rats. Whether this finding is relevant to the human situation remains uncertain.

Apart from the relative proportion of saturated and polyunsaturated fatty acids, the FFA/albumen ratio (Willebrands, Ter Welle & Tasseron, 1973) and the duration of exposure to the FFA (Coraboeuf, Deroubaix, Karagueuzian, de Leiris & Pennec, 1978) undoubtedly play an important role in determining the incidence of cardiac arrhythmias.

It is believed that the last fat put into store is the first mobilized into the blood. Consequently when polyunsaturated fat is consumed in the diet it may not only prevent the development of atherosclerosis but also may have a protective action against the development of cardiac arrhythmias in so far as a considerable proportion of the free fatty acids mobilized during the severe stress induced by a cardiac infarction would be polyunsaturated.

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