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ACTIONS OF PROSTAGLANDIN PRECURSORS AND OTHER UNSATURATED FATTY ACIDS ON CONDUCTION TIME AND REFRACTORY PERIOD IN THE CAT HEART *in situ*

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1 The effect of arachidonic, dihomo-γ-linolenic, linoleic, α-linolenic and oleic acid, given by intravenous infusion, on conduction time and functional refractory period have been studied in the cat heart *in situ*.

2 The prostaglandin precursors, arachidonic acid and dihomo-γ-linolenic acid, prolonged the conduction time and the functional refractory period. Linoleic acid was also effective but to a lesser degree. α-Linolenic acid and oleic acid showed no or only a weak effect in this respect.

3 Pretreatment with indomethacin diminished or abolished the actions of the three effective fatty acids but not those of prostaglandin E_2.

4 The results suggest that the effects of prostaglandin precursors on conduction time and refractory period are responsible for their antiarrhythmic effectiveness and that these effects are attributable to their endogenous conversion into prostaglandins.

Introduction

Several authors have discussed the connection between a high plasma level of free fatty acids and the risk of arrhythmias in myocardial infarction (Oliver, Mjøs & Rowe, 1974; Opie & Lubbe, 1975). However, the findings obtained in animal experiments on the influence of fatty acids on cardiac rhythm are still at variance. Thus Henderson, Most, Parmley, Gorlin & Sonnenblick (1970), Kurien, Yates & Oliver (1971) and Willebrands, ter Welle & Tasserson (1973) showed that fatty acids were arrhythmogenic, whereas Opie, Morris, Thomas, Holland, Owen & van Norden (1971), Kostis, Mavrogeorgis, Horstmann & Gotzoyannis (1973) and Most, Capone & Mastrofrancesco (1976) found no arrhythmogenic effect even with high concentrations of circulating fatty acids.

Electrophysiological investigations by Borbola, Papp & Szekeres (1974) and by Wasilewska-Dziubinska, Czarnecka, Beresewicz & Lewartowski (1975), using isolated Purkinje fibres of the calf and isolated hearts of guinea-pigs, respectively, showed evidence of a direct arrhythmogenic effect of octanoate and palmitate. On the other hand antiarrhythmic properties have been demonstrated with some prostaglandins as well as with arachidonic and linoleic acids in a variety of experimental arrhythmias in a number of different species (Zijlstra, Brunsting, ten Hoor & Vergroessen, 1972; Mest, Schrör & Förster, 1973; Mest & Förster, 1973; 1975; Mentz & Förster, 1974a,b; Förster, Mentz, Blass & Mest, 1976; Mest, Blass & Förster, 1976; 1977). A depression of conduction and a prolongation of the functional refractory period can suppress arrhythmias of different origin (Hoffmann & Cranefield, 1964; Basset & Hoffman, 1971; Giardina & Bigger, 1973). Therefore the antiarrhythmic effectiveness of prostaglandins *in vivo* might be attributed to their depressive actions on conduction time and refractory period described by Bayer, Förster & Sperling (1976). The small and non-uniform cardiac membrane effects *in vitro* (Kecskemeti, Kelemen & Knoll, 1973; Förster, Borbola, Papp, Schrör & Szekeres, 1974; Bayer *et al.*, 1976) are unlikely to account for the antiarrhythmic effectiveness of these fatty acids *in vivo*. The precursor of both prostaglandin E_2 (PGE_2) and $PGF_{2\alpha}$ arachidonic acid (for references see Flower, 1974; van Dorp, 1976) has similar effects to PGE_2 and $PGF_{2\alpha}$ on the transmembranal action potential of the guinea-pig myocardium (Szekeres & Papp, 1976). However, there have been no investigations into the actions of prostaglandin precursors and of other fatty acids on conduction time and refractory period in the heart *in situ*. We have therefore investigated the actions of the prostaglandin precursors, arachidonic acid and dihomo-γ-linolenic acid (Flower, 1974; van Dorp, 1976), as well as some other unsaturated fatty acids (linoleic acid, α-linolenic acid, oleic acid), on conduction time and refractory period of the cat heart *in situ*. In addition, we examined whether inhibition of prostaglandin biosynthesis by indomethacin (Flower, 1974) influences the electrophysiological effects of these precursors, in

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view of the finding that the antiarrhythmic effects of arachidonic acid are greatly diminished after indomethacin pretreatment (Förster *et al.*, 1976; Mest *et al.*, 1977).

Methods

Cats of either sex, ranging in weight from 2.0 to 4.0 kg were anaesthetized with sodium pentobarbitone (35 mg/kg i.p.). The animals were artificially ventilated and prepared as described previously (Bayer *et al.*, 1976). The hearts were driven by an electrode clamped on the left auricle (square wave pulses, 1 ms duration, twice threshold current, driving frequency about 20% above spontaneous frequency). Action potentials were recorded from the right auricle and the right ventricle by bipolar silver electrodes. The period between the trigger pulse and the atrial action potential is defined as intra-atrial conduction time (AC), between the trigger pulse and the ventricular action potential as atrioventricular conduction time (AVC) (Szekeres & Papp, 1971). After each fourth trigger pulse a premature test stimulus (square wave pulses, 1 ms duration, 1.5 times threshold current) was applied and the interval between this stimulus and the preceding trigger pulse was progressively prolonged. The earliest test stimulus that elicited atrial and ventricular action potentials was determined. The minimal interval between two atrial action potentials and two ventricular action potentials is defined as the functional refractory period of the atrium (ARP) and of the atrioventricular conducting system (AVRP), respectively (Cagin, Kunstadt, Wolfish & Levitt, 1973).

The fatty acids were infused intravenously as the sodium salts for 5 min and the effects were measured between 30 s and 20 min after starting the infusion. In a number of cats the biosynthesis of prostaglandins was inhibited by indomethacin 10 mg/kg, injected intravenously 90 min before the infusions of fatty acids. The investigations were carried out on 66 cats (39

Table 1 Actions of arachidonic acid (AA), dihomo-γ-linolenic acid (DLLA), linoleic acid (LA) and prostaglandin E_2 (PGE_2) before, and after, indomethacin pretreatment and of α-linolenic acid (α-LLA), oleic acid (OA) and indomethacin on intra-atrial conduction time (AC), atrioventricular conductan time (AVC), functional refractory period of atrium (ARP) and functional refractory period of atrio-ventricular conducting system (AVRP) in the cat heart *in situ*

Compound/dose	*AC*	*AVC*	*ARP*	*AVRP*
Control level (ms) (n = 16)	41.3 ± 1.9	104.3 ± 2.9	152.3 ± 6.5	185.2 ± 5.2
AA (n = 10) 1 mg kg^{-1} min^{-1}	6.1 ± 1.1*	13.9 ± 2.1*	12.8 ± 2.0*	10.1 ± 1.5*
AA (n = 9) after indomethacin	3.2 ± 1.4*	2.0 ± 2.3**	3.5 ± 1.7*,**	3.3 ± 1.3*,**
DLLA (n = 7) 2 mg kg^{-1} min^{-1}	7.1 ± 4.6	11.3 ± 4.1*	16.6 ± 3.4*	10.6 ± 2.5*
DLLA (n = 7) after indomethacin	1.4 ± 2.9 (shortening)	3.5 ± 4.1	6.6 ± 1.7*,**	2.9 ± 2.1**
LA (n = 9) 2 mg kg^{-1} min^{-1}	5.9 ± 1.3*	6.8 ± 1.2*	6.7 ± 1.6*	5.0 ± 0.8*
LA (n = 10) after indomethacin	2.6 ± 0.8*,**	4.8 ± 0.9*	4.9 ± 1.4*	3.0 ± 0.7*,**
PGE_2 (n = 8) 5 µg kg^{-1} min^{-1}	6.8 ± 1.0*	15.0 ± 5.9*	15.8 ± 4.2*	12.1 ± 5.7*
PGE_2 (n = 7) after indomethacin	8.9 ± 1.4*	16.2 ± 4.0*	10.4 ± 2.3*	11.7 ± 2.6*
α-LLA (n = 7) 2 mg kg^{-1} min^{-1}	1.2 ± 2.5	2.9 ± 1.9	3.4 ± 1.8	0.5 ± 1.8
OA (n = 9) 2 mg kg^{-1} min^{-1}	3.0 ± 1.1*	3.2 ± 1.2*	2.9 ± 0.9*	2.0 ± 1.1
Indomethacin (n = 9) 10 mg/kg	2.5 ± 2.0	2.9 ± 2.8	5.6 ± 3.0	3.8 ± 2.5

Means of maximal percentage prolongation ± s.e. mean, n = number of effects in n-several cats.
* Different from control values ($P < 0.05$); ** different from values without indomethacin pretreatment ($P < 0.05$).

animals without and 27 animals with indomethacin). Each fatty acid was usually given once only to each animal. Statistical significance was calculated by Student's t test. Mean values of the maximal percentage changes in comparison with controls before or after indomethacin, respectively, ± s.e. are given.

Substances used were sodium pentobarbitone (Abbott), arachidonic acid (AA, 20:4ω6, Unilever), dihomo-γ-linolenic acid (DLLA, 20:3ω6, Upjohn), α-linolenic acid (α-LLA, 18:3ω3, Karl Roth OHG), linoleic acid (LA, 18:2ω6, Karl Roth OHG), oleic acid (OA, 18:1ω9, Merck), prostaglandin E_2 (PGE_2, Upjohn), indomethacin (Chinoin).

Results

Infusions of both the prostaglandin precursors AA (1 mg kg^{-1} min^{-1}) and DLLA (2 mg kg^{-1} min^{-1}) prolonged AC, AVC, ARP and AVRP in the cat heart *in situ*. Both fatty acids in the dose used were as effective as infusions of 5 μg kg^{-1} min^{-1} PGE_2 (Table 1). LA (2 mg kg^{-1} min^{-1}) also prolonged these parameters but to a lesser degree (Table 1). On the other hand, α-LLA (2 mg kg^{-1} min^{-1}) and OA (2 mg kg^{-1} min^{-1}) had no effect or a poor effect (Table 1). The effects of the fatty acids began between the 2nd and the 3rd min after starting the infusions and reached a maximum between 5 and 8 min. These parameters then tended to return towards control levels although 15 min after starting the infusions the effects were still evident ($P < 0.05$). After 20 min, the values were similar to control ($P > 0,1$). AA and DLLA lowered the blood pressure by 21.2 ± 5.6% and 12.2 ± 4.0% ($n = 8$; $P < 0.05$), respectively. After this initial decrease (maximal in the 2nd min after starting the infusions) there was an increase of blood pressure above control which usually persisted up to 20 min after starting the infusion (AA: + 6.6 ± 3.8%, $P > 0.1$; DLLA: +21.5 ± 5.5%, $P < 0.05$). LA, α-LLA and OA did not influence the blood pressure significantly ($P > 0.1$).

Indomethacin 10 mg/kg did not influence AC, AVC, ARP or AVRP ($P > 0.1$; Table 1). Indomethacin increased the blood pressure by 14.3 ± 4.8% ($n = 9$, $P < 0.05$). The maximal effect was reached after about 15 min. At 1 h after administration of indomethacin the blood pressure was normal. After indomethacin pretreatment the actions of the three effective fatty acids on AC, AVC, ARP and AVRP were greatly diminished or abolished (Table 1). However, the inhibitory effect of PGE_2 (5 μg kg^{-1} min^{-1}) on these electrophysiological parameters was not influenced by indomethacin pretreatment (Table 1). There were no difference in the effect of AA, DLLA and LA on systemic arterial pressure before or after indomethacin pretreatment ($P > 0.1$).

Discussion

The unsaturated fatty acids AA, DLLA, LA, α-LLA and OA investigated in this study had different effects on conduction time and functional refractory period in the cat heart *in situ*. AA, DLLA and to a lesser degree LA prolonged significantly AC, AVC, ARP and AVRP. On the other hand α-LLA and OA were practically ineffective in this respect, although OA prolonged AC, AVC and ARP to a slight extent also.

The prostaglandin synthetase inhibitor, indomethacin, greatly reduced the effects of AA, DLLA and LA on AC, AVC, ARP and AVRP in the cat heart, while the effects of PGE_2 were not influenced.

Mest & Förster (1973), Förster *et al.* (1976) and Mest *et al.* (1977) showed that AA and LA were effective against several experimentally induced arrhythmias, whereas α-LLA and OA were without effect. In this study the antiarrhythmic effectiveness of DLLA has also been investigated. The antiarrhythmic effectiveness of AA and LA was greatly inhibited by indomethacin pretreatment (Förster *et al.*, 1976; Mest *et al.*, 1977). These investigations included experiments on $BaCl_2$-induced arrhythmias in rabbits, and ouabain-induced arrhythmias in guinea-pigs and in cats.

Qualitatively similar cardiac effects of prostaglandins and of prostaglandin-precursors have been described: (a) prostaglandins (Mest *et al.*, 1973; Mentz & Förster, 1974a, b; Mest & Förster, 1975) and prostaglandin-precursors (Mest & Förster, 1973; Förster *et al.*, 1976; Mest *et al.*, 1977) are antiarrhythmic; (b) prostaglandins (Bayer *et al.*, 1976) and prostaglandin-precursors (this study) prolong conduction time and the refractory period of the heart *in situ*; (c) prostaglandins (Kecskemeti *et al.*, 1973; Förster *et al.*, 1974; Bayer *et al.*, 1976; Tanz, Robbins, Harwood & Rightmeier, 1977) and AA (Szekeres, Borbola & Papp, 1976) have relatively minor direct cardiac membrane actions.

On the other hand a number of other fatty acids are arrhythmogenic or do not have any marked influence on the cardiac function (see Introduction).

We suggest that the inhibitory effects of AA and LA on conduction time and functional refractory period described in this study are probably responsible for their antiarrhythmic activity.

The similar cardiac effects and the antiarrhythmic activity of both prostaglandins and their precursors, the inhibition of the antiarrhythmic effects of prostaglandin-precursor fatty acids by indomethacin and the lack of antiarrhythmic effects of nonprecursor fatty acids justify the conclusion that the prostaglandin-precursors themselves do not act on the heart but the prostaglandins biosynthesized from them.

Although only AA and DLLA are natural prostaglandin-precursors, LA is also involved in reactions

leading to the formation of prostaglandins (Flower, 1974; van Dorp, 1976). However, there are publications which indicate that the cat lacks a number of desaturases so that LA cannot be converted to the direct precursors AA and DLLA (Rivers, Sinclair & Crawford, 1975; Hassam, Rivers & Crawford, 1977; Frankel & Rivers, 1978). In our investigations, LA showed the same properties as AA and DLLA but to a lesser degree. Therefore we would suggest that the cat can biosynthesize prostaglandins although to a minor extent, because indomethacin diminished the LA effects. The discrepancies between our pharmacological results and the findings of Crawford's group remain unexplained at the present time.

Our finding that the vasodepressor response of AA and DLLA was not inhibited by indomethacin pretreatment is difficult to interpret. Most authors assume that AA exerts this effect through its conversion into PGE_2 since pretreatment with indomethacin inhibited the AA-induced vasodepressor action (Cohen, Sztokalo & Hinsch, 1973; Larsson & Ånggard, 1973; Rose, Johnson, Ramwell & Kot, 1974). On the other hand Wennmalm (1977) did not find any inhibitory action of indomethacin pretreatment on the vasodilator AA effect in man. The dose of indomethacin used in our experiments should have been sufficient to inhibit prostaglandin biosynthesis by 70 to 100% for 24 h (Flower, 1974). Possibly the vasodilator effect of AA, and perhaps also of DLLA, is only partly due to conversion to prostaglandin (Wennmalm, 1977).

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