INFLUENCE OF FATTY ACIDS ON PRESSOR RESPONSES TO CATECHOLAMINES

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Summary: Lauric, Myristic and Palmitic acids had no appreciable effect whereas Stearic,, Oleic and Linoleic acids caused some reduction in dog blood pressure. Pressor responses to epinephrine and nor-epinephrine were potentiated whereas the depressor response to isoproterenol was reduced during the infusion of fatty acids in dogs. ACTH alone, which causes mobilization of free fatty acids had no appreciable effect on blood pressure responses to catecholamines, however, its administration followed by salicylate produced marked potentiation of the pressor responses to epinephrine and nor-epinephrine; the depressor response to isoproterenol was reduced.

Key words: fatty acids ACTH salicylate catecholamines blood pressure

INTRODUCTION

Lipids play an important role as energy source in cardiac function (7). Recently the fatty acids have been reported to induce cardiac stimulation in frogs and rabbits (2,3). The fatty acids remain attached for a long period to the blood vessels presumably in a bound state (1), however, the impact of such interaction on circulatory system has yet to be revealed. This presentation, therefore, explores the influence of fatty acids on the pressor responses to catecholamines.

MATERIALS AND METHODS

Dogs of either sex weighing between 10 to 15 *kg* were anaesthetized with phenobarbitone sodium (150 *mg*/*kg* i.p.). The trachea was cannulated and systemic blood pressure was recorded from carotid artery by means of a mercury manometer. Both femoral veins were cannulated for intravenous injections. The responses to varying doses (0.2 - 1.0 $\mu g/kg$) of epinephrine (E), norepinephrine (NE) and isoproterenol (ISO) were recorded before and 10, 50 and 100 minutes after fatty acid infusion at a rate of 0.1 *ml*/*kg*/min (about 0.1 *mg*/*kg*/min) with the help of continuous slow injector (Inco slow injector).

The responses to catecholamines were also recorded after infusion of a mixture of equimolar concentration of fatty acid and albumin.

The control group received the influsion of normal saline at corresponding level. Separate groups of ten animals were employed for each fatty acid.

In a separate set of experiments the influence of endogenous mobilization of free fatty acids (FFA) by ACTH and salicylate treatment on pressor responses to catecholamines was studied. After control responses to catecholamines (0.2 - 1.0 $\mu g/kg$) had been recorded, ACTH (1 - 10 *I.U./kg* i.m.) was injected. To another group injection of ACTH followed by sodium salicylate (50 - 300 *mg/kg* i.v.) was given. The pressor responses to catecholamines were recorded immediately and at every 30 minutes interval for three hours after the treatment with these drugs. Salicylate are known to displace FFA from its protein complex and, therefore, were employed in the study. Salicylate control group was used for comparison.

The four millimolar solutions of salts of fatty acids were prepared by dispersing suitable amount of fatty acids in water by sonication (Vibronix), adjusting the pH to 7.4 with sodium hydroxide and resonicating the mixture.

RESULTS

FFA Infusion : Stearic, oleic and linoleic acids caused some reduction in canine blood pressure but lauric, myristic and palmitic acids had no appreciable effect. Bovine albumin *per se* or the solutions of fatty acids mixed and incubated with bovine albumin were without any effect on blood pressure.

When the responses to E, NE and ISO were tested during the infusion of the fatty acids (Table I), a significant modification in the pressor responses to all the catecholamines was observed. The actions of E and NE were significantly ($P < 0.05$) potentiated whereas the action of isoproterenol was inhibited by infusion of all the fatty acids. The ability of different fatty acids to modify the pressor response to catecholamines differed quantitatively. Appreciable potentiation of action of E and NE was observed after 1.0 *mg/kg* (1.0 *ml/kg*) of laurate and myristate. In case of others similar potentiation could be seen only after administration of 5 *mg/kg*. The maximal potentiation in responses to E and NE was observed at 5 *mg/kg* in case of lauric and myristic acids and after 10 *mg/kg* in case of other fatty acids. The maximal inhibitory effect against ISO was, however, seen with 10 *mg/kg* of all fatty acids. The normal saline control did not exhibit appreciable change in the usual responses to E, NE and ISO even after large infusion for corresponding periods. These effects were absent when fatty acids were tested after mixing with albumin.

Effect of ACTH and Salicylate: Pressor responses to catecholamines were not altered much by prior treatment with ACTH salicylate except that the responses recorded after the administration of salicylate were slightly prolonged as compared to control ones.

TABLE I: Catecholamine (1 $\mu g/kg$) induced change in mean arterial blood pressure (mm/Hg) during continuous infusion of fatty acids.

FFA 4 *mM*	*Epinephrine*				*Norepinephrine*				*Isoproterenol*			
	Total quantity of FFA infused mg/kg											
	0 *mg*	1 *mg*	5 *mg**	10 *mg**	0 *mg*	1 *mg*	5 *mg**	10 *mg**	0 *mg*	1 *mg**	5 *mg**	10 *mg**
Oleate	65.0 ±1.1	67.1 ±1.0	75.0 ±0.9	78.0 ±0.9	88.1 ±0.6	91.0 ±0.5	99.0 ±1.1	103.0 ±1.3	80.0 ±1.0	74.1 ±0.9	65.1 ±0.8	50.2 ±1.2
Linoleate	62.0 ±1.5	65.5 ±1.6	76.5 ±1.4	81.0 ±1.0	85.1 ±0.8	87.5 ±0.8	95.0 ±0.8	101.0 ±0.9	77.3 ±0.9	70.0 ±0.7	59.1 ±0.5	50.0 ±0.7
Laurate	64.9 ±1.0	70.0* ±1.0	78.1 ±1.8	74.0 ±0.8	87.0 ±1.0	97.2* ±1.7	117.1 ±0.9	102.0 ±2.0	79.4 ±0.8	65.0 ±3.0	57.2 ±1.5	42.3 ±2.8
Myristate	66.1 ±1.2	78.4* ±1.0	90.0 ±1.0	83.5 ±2.0	88.0 ±1.2	98.0* ±0.8	109.0 ±0.5	107.2 ±1.0	80.0 ±1·0	70.2 ±1.0	55.1 ±0.6	47.0 ±1.5
Palmitate	64.9 ±1.3	65.0 ±1.5	75.2 ±3.0	86.2 ±1.0	87.8 ±1.2	89.8 ±2.0	106.0 ±0.8	109.0 ±0.7	78.8 ±1.0	68.2 ±1.8	57.1 ±0.9	45.0 ±1.7
Stearate	64.0 ±1.0	67.1 ±0.6	78.0 ±1.6	86.2 ±1.2	87.5 ±1.2	90.1 ±1.4	98.0 ±1.0	104.0 ±0.6	80.0 ±1.0	71.0 ±1.3	60.0 ±1.2	46.5 ±1.0

± Standard error of mean of five observations.

* The difference between the control and experimental values were found to be significant ($P < 0.05$).

Administration of ACTH followed by sodium salicylate led to significant alterations, in pressor responses to catecholamines (Table II). The pressor responses to E and NE were markedly potentiated whereas the depressor response to ISO was significantly reduced. Such phenomena persisted for as long as three hours from the time of administration of salicylate after ACTH. Canine blood pressure levels, however, were not altered.

TABLE II: Change in mean arterial blood pressure by (mm/Hg) catecholamines in dogs after treatment with ACTH (2 I.U/kg) followed by Sodium Salicylate (50 *mg/kg*).

	Time in hours				
Drug 1 *μg/kg*	0	1/2	1	2	3
E	65.0 ± 1.5	75.1 ± 0.7	85.1 ± 0.5	85.0 ± 0.7	80.0 ± 0.8
NE	84.0 ± 1.0	95.0 ± 0.5	101.0 ± 0.9	101.0 ± 1.1	99.2 ± 1.0
ISO	78.2 ± 1.0	72.1 ± 0.7	62.0 ± 1.3	56.1 ± 1.0	51.0 ± 0.5

± Standard error of mean of five observations.
The differences between the control and experimental values in all cases found to be significant ($P<0.05$)
E = Epinephrine, NE = Norepinephrine, ISO = Isoproterenol

DISCUSSION

All the fatty acids were found to potentiate the pressor responses to E and NE and inhibit the depressor response to ISO, the intensity of their effect being dependent on the amount of fatty acid infused. It must be pointed out that the resting or the basal blood pressure levels had also decreased as a result of fatty acid infusion. The possible effect of the variation in the initial blood pressure levels on the pressor responses is not well described. Our previous findings in frog and mammalian heart (2, 3) as well as present findings on vascular system afford direct evidence indicating the importance of fatty acids in the regulation of cardiovascular functions. The mechanism whereby these effects are mediated remains in the realm of speculation. Fatty acids in their anionic state exert a number of toxic reactions such as haemolysis of red cells (12), uncoupling of oxidative phosphorylation (8), activation of Hageman factor to accelerate thrombus formation (9) and inhibition of bacterial growth (5). These phenomena are presumably induced by the interaction of fatty acid anions with cellular or enzyme proteins. Albumin by complexing with fatty acids mask their toxic actions by disallowing them to react randomly with any other material in circulation or tissue materials (5,10). Actions resulting from the administration of high doses of fatty acids in their salt form such as vasodepression, potentiation of an adrenergic pressor responses and inhibition of β-adrenergic depressor responses in intact animals are absent if mixture of fatty acid and albumin is infused. These observations explain the absence of toxic

actions of fatty acids even though the circulating fatty acid blood concentrations are raised very high by number of factors since their transport occurs in mostly albumin bound form (14). It is evident from the present studies that treatment with a hormone like ACTH which is potent mobiliser of FFA (13) from fat stores fails to evoke any action on pressor responses to catecholamines presumably due to the fact that the circulating high levels of FFA are still in the form of albumin - FFA complex and do not interact with the cardiovascular system.

Salicylates can release some normal metabolites including L-tryptophan (15) and uric acid (16) from their binding sites on plasma proteins and thus affect their rate of entry into the tissues. Dawkins *et al* (4) have recently demonstrated that salicylate causes release of palmitic, stearic, oleic and linoleic acids from binding sites on human plasma protein and bovine albumin. The magnitude of the effect although small in relation to the amount of protein bound fatty acids, represented a tenfold rise in the concentrations of fatty acids which are free in solution. The authors have explained several reported actions of salicylates on fatty acid metabolism in men and in experimental animals. Some of the actions like uncoupling of oxidative phosphorylation caused by salicylates could be due to the liberation of fatty acid, since fatty acids are known to induce similar phenomenon. Salicylate as such remained without exerting any action on pressor responses to catecholamines. The marked potentiation in pressor responses to catecholamines after ACTH induced mobilization followed by salicylate administration could have coccured due to the displacement of FFA in their anionic state from protein to which they are bound and their interaction with the cardiovascular system. Fatty acids being surfactants possess the property of directly acting upon the cellular memberane and increase the permeability (6,11). The earlier report indicates the enhanced exchange of electrolytes in presence of the fatty acids (2).

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