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Effect of lysolecithin on the systemic arterial blood pressure of anaesthetized rats

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Lysolecithin (LPC), a naturally occurring glycerophosphatide found in various tissues and fluids, has strong haemolytic activity. It is formed by hydrolysis of lecithin by phospholipase A_2 with liberation of fatty acids.

Middleton & Phillips (1963) reported that LPC causes non-competitive inhibition of the effects of various stimuli on smooth muscle. From this finding LPC might be expected to influence the cardiovascular system of animals. Khairallah & Page (1960) reported that a preparation obtained from dog incubated plasma had a pressor effect on anaesthetized rats and suggested that the effect was due to LPC; conversely they found that synthetic stearoyl-LPC elicited a depressor response in the rats. Since the vasoactivity of LPC is uncertain, we have examined the vaso-activities of LPC with various fatty acid moieties on the systemic arterial blood pressure of anaesthetized rats.

Male Wistar strain rats, 240–260 g, were anaesthetized with sodium pentobarbitone (40 mg, kg^{-1}, i.p.). The arterial blood pressure was recorded through a cannula in the left carotid artery with a mercury manometer or a pressure transducer (Nihon Kohden MPU-0·5) coupled to a multipurpose polygraph (Nihon Kohden RM-45). The heart rate was recorded with a cardiotachometer triggered by the arterial pressure wave. Test substances in 0·15 ml of physiological saline (0·9% w/v, NaCl solution) were injected into the left femoral vein through a cannula and the cannula was then flushed with 0·1 ml of saline. When necessary, emulsions of substances were prepared by sonication (e.g. stearoyl-LPC).

Lauroyl-, myristoyl- and palmitoyl-LPC(1-acyl-*sn*-glycero-3-phosphocholine) and didecanoyl- and distearoyl-lecithin(1,2-di-acyl-*sn*-glycero-3-phosphocholine) were purchased from Sigma Chemical Co. (St. Louis, Mo.). Oleoyl-, linoleoyl- and linolenoyl-LPC were supplied from Sardary Research Laboratories (London, Ontario, Canada). Didecanoyl- and distearoyl-lecithin were hydrolysed with phospholipase A_2 (Bee Venom, Sigma) to the respective LPCs as described by Shipolini et al (1971). Before use, the purity of each LPC was confirmed by t.l.c. and fatty acid analysis was carried out by gas chromatography on samples prepared by methanolysis. Values are given as means (± s.e.m.) of results in at least five experiments unless otherwise stated.

On intravenous administration all the LPCs tested decreased both the systolic and diastolic arterial blood pressure, and none of the compounds had the pressor activity suggested by Khairallah & Page (1960).

The log dose-depressor response relation of saturated LPCs are shown in Fig. 1.

Both the depressor responses and their durations

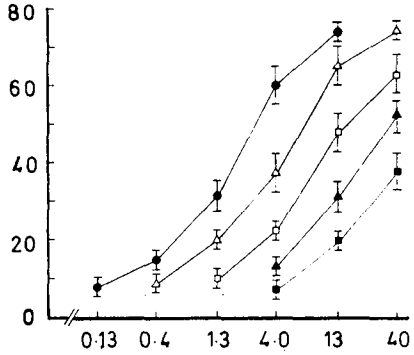

FIG. 1. Dose-response relation of saturated LPCs. The fatty acid composition of the LPCs is indicated by: ■ $C_{10:0}$, □ $C_{12:0}$, ● $C_{14:0}$, △ $C_{16:0}$, ▲ $C_{18:0}$. Results are expressed as means ± s.e.m. Ordinate: Decrease in carotid arterial blood pressure (mm Hg). Abscissa: Intravenous lysophosphatidyl choline (μmol kg^{-1}).

* Correspondence.

were dose-dependent, and no tachyphylaxis or sensitization was observed.

The dose-response curves of the respective LPCs were similar in shape and parallel to each other. Of the five saturated LPCs with $C_{10:0}$ to $C_{18:0}$ fatty acids, myristoyl-LPC had the strongest effect and decanoyl-LPC had the weakest. Myristoyl-LPC had 2–4 times more effect than palmitoyl-LPC and about 20 times more effect than decanoyl-LPC. With increase or decrease of the hydrocarbon chain length of the fatty acid residue from $C_{14:0}$, the depressor activity of the LPCs progressively decreased. Introduction of a cis-double bond into the fatty acid hydrocarbon chain resulted in decrease in hypotensive activity (Fig. 2). Among LPCs with saturated or unsaturated C_{18} fatty acids, stearoyl-LPC($C_{18:0}$) had the most effect, followed by oleoyl-LPC($C_{18:0}$). Oleoyl-LPC had 5–10 fold more effect than linoleoyl-LPC($C_{18:2}$) and 30 fold more effect than linolenoyl-LPC($C_{18:3}$). Oleoyl-LPC had only about one 30th as much activity as myristoyl-LPC which was the strongest depressor among the tested compounds.

Occasionally a depressor response elicited by linoleoyl- or linolenoyl-LPC was followed by a rise in blood pressure. A typical recording of the blood pressure and

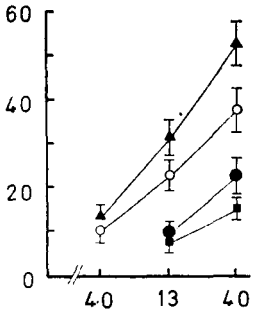

FIG. 2. Dose-response relation of unsaturated LPC(C_{18})s. The fatty acid composition of the LPCs is indicated by: ▲ $C_{18:0}$ ○ $C_{18:1}$ ● $C_{18:2}$ ■ $C_{18:3}$ Results are expressed as means ± s.e.m. Ordinate and abscissa as for Fig. 1.

the heart rate with myristoyl-LPC is shown in Fig. 3. Slight reduction in the heart rate was observed with the hypotension induced by myristoyl-LPC (4 μmol, kg^{-1}).

Preliminary studies suggested that the hypotensive effects of LPCs in anaesthetized rats are not mediated *via* the autonomic nervous system, but are due to direct effects on the peripheral vascular system.

Palmitoyl- or stearoyl-LPC had strong haemolytic effects on erythrocytes and oleoyl-LPC also had some haemolytic effect (Reman et al 1969). The hypotensive effect and the haemolytic effect were reduced in parallel by incorporation of an unsaturated bond into the fatty acid moiety. The hypotensive activity of LPC is probably ascribable to its characteristic wedge-shaped molecular structure.

Certain other vaso-active lyso-type phospholipids have been reported. Turcotte et al (1973), Bunag & Walaszek (1973) and Antonello et al (1973) showed that lysophosphatidyl ethanolamines showed depressor effects in rats with acute or chronic renal hypertension. Recently the unique vasoactivity of lysophosphatidic acid (LPA, 1-acyl-*sn*-glycero-3-phosphate) (Tokumura et al 1978a, b, c) was reported from our laboratory. LPA had a strong pressor effect in rats but a depressor effect in cats. It seems possible that the substance with pressor activity in rats reported by Khairallah & Page (1960) might be LPA formed by activated phospholipase A_2 or D, because synthetic LPCs elicited no pressor responses in rats, as described above.

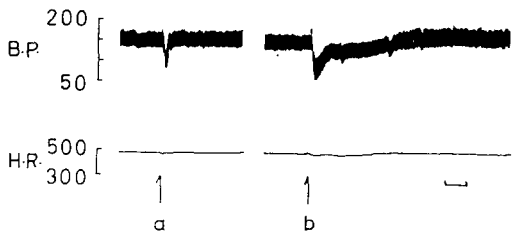

FIG. 3. Blood pressure responses of an anaesthetized rat to intravenous injections of myristoyl-LPC. The rat was anaesthetized with sodium pentobarbitone (40 mg kg^{-1}, i.p.). Arrows indicate the points of injections of the samples. Upper trace shows the blood pressure (BP) (mm Hg) responses. Lower trace shows the heart rate (HR) (beats min^{-1}). a 1.3; b 4 μmol kg^{-1}. Horizontal scale: 1 min.

LPC does not have strong hypotensive activity but this activity may have a significant physiological action on the cardiovascular system, because LPC is widely distributed in the animal body.

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