Physiological and Clinical Importance of Lipoprotein(a)

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(Received May 24, 1990; Accepted May 24, 1990)

Lipoprotein(a) is a genetically regulated trait, and its concentration in serum seems to be independent from that of other lipoprotein classes. It can be detected by ultracentrifugation in the d = 1.05 - 1.12 g/ml density range. Based on epidemiological observations Lp(a) is an independent risk factor for coronary heart disease. Its structure resembles LDL, but contains, in addition to apolipoprotein B 100, the disulphide-linked apoprotein(a). Apoprotein(a) shares a striking homology with plasminogen, consisting multiple repeating domains similar to kringle IV, a single kringle V and an inactive protease segment. The heterogeneity of Lp(a) complex is determined by the apoprotein(a) moiety. It seems so, that atherogenic properties of Lp(a) can be explained by its binding to glycosaminoglycans and inhibition of fibrinolysis. This latter effect is carried out by the kringle domains, which can interact with the plasminogen activators and plasmin binding sites on endothelial surface.

The atherogenic properties of Lp(a) are expressed over 30 mg/dL serum concentration. Well-known antilipidemic drugs do not affect its serum level and genetically determined phenotype. Diseases leading to secondary hyperlipoproteinemia may influence the lipoprotein(a) level, too.

(Key Words: Lipoprotein(a), atherosclerosis, fibrinolysis)

Based on epidemiological data, there are a lot of evidences available that serum cholesterol level correlates with the incidence of cardiovascular disease, particularly with the manifestation of coronary heart disease (CHD) (7, 9). As it was shown by the practical observations of bedside physicians, in part of patients with CHD the serum cholesterol and even the serum triglyceride concentrations are not elevated and can be detected within the normal range. This, in fact, was demonstrated at first by Nikkilä in 1953 using paper electrophoresis for analysing the lipoproteins (18). He found a decreased alpha-lipoprotein level in patients suffering from CHD and with normal serum cholesterol and triglyceride levels. In the last decade the new discoveries of lipoprotein metabolism have shed some more light on the possible role of apolipoproteins and lipoprotein subfractions in the atherogenic process.

In 1963 Berg found by the use of immunological methods a new serum type system that he called lipoprotein(a) (2). He found this serum lipoprotein fraction to be present in about one third of Northern Europeans population. Formerly he screened the sera by double immunodifussion method, which has been proved to be very insensitive and it was able to detect the presence of Lp(a) lipoprotein in subjects only over a given concentration limit. Berg and Dahlen called the attention to the relationship between lipoprotein(a) and the occurrence of prebeta lipidprotein band during agarose gel electrophoresis of patients with CHD (3). The development of techniques in lipoprotein research led to understand some of the most important properties of Lp(a). Albers and coworkers have shown by the use of radioimmunoassay method that Lp(a) can be detected in more than 90% of healthy subjects (1).

The structure and metabolism of Lp(a)

The Lp(a) lipoprotein consists of two polypeptide chains, which bind lipids and sugar
molecules. The main apoprotein moiety of it is the same as for LDL, the apoprotein B 100 (Fig. 10). This apoprotein is known as the most atherogenic factor in blood and is bound by one or more disulphide bridge(s) to apolipoprotein(a), which determined the specific physiological properties of the Lp(a) complex. Measuring the molecular weight the Lp(a) is thought to be one of the biggest proteins in the human serum. After reduction, running on polyacrylamide gelelectrophoresis followed by transferring to nitrocellulose sheet it can be seen that sera of different individuals contain apolipoprotein(a) differing in size and electrophoretic mobility (Fig. 1). The molecular weight of of apoprotein(a) may be higher than, equal to, or lower than that of apoprotein B 100, which is about 550 kD (6, 22, 23) (Fig. 2). This size heterogeneity is thought to be related to the length of polypeptide chains, because it is not affected by the removal of sialic acid content by neuraminidase digestion.

McLean and coworkers showed at first by investigation the cloned DNA of Lp(a) that it contains a long chain of special polypeptide rings, so called kringle, which show a very strong similarity with the same structures of plasminogen (16). Apoprotein(a) consists f 37 copies of kringle IV, one of kringle V and the protease domain, which can not be activated like in plasminogen, because the arginine aminoacid at the cleavage site for activation is changed for serin. Carrying the characteristic lysine binding sites, the Lp(a) can be removed totally from the serum by the use of lysine-Sepharose column chromatography during the same procedure as plasminogen (12).

The physiological role of Lp(a) is unknown. Its synthesis sites may be in the liver as it was shown by demonstrating the messenger RNA

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**Fig. 1** SDS-polyacrylamide (3.75%) gelelectrophoresis of different serum samples and purified Lp(a) followed by western blotting and detection by polyclonal anti-Lp(a) antibody.

Lane A: purified Lp(a) complex
Lane B: serum of patients with high Lp(a) concentration (patient A) after reduction
Lane C: serum of patients B with high Lp(a) concentration after reduction
Lane D: purified Lp(a) from patient B
Lane E: delipidized serum of patient B (reduced)
1: Lp(a) complex; 2: apoprotein(a) of patients B; 2': apoprotein(a) of patient A; 3: apoprotein B 100 4: reduced plasminogen
of Lp(a) in the liver cells and the change of Lp(a) phenotype of recipient for that of donor after liver transplantation (24). Using sequential ultracentrifugation and immunochemical method the intracellular presence of lipoprotein(a) in liver cells could be demonstrated (Császár, Dieplinger and Utermann, unpublished data, personal communication). Kostner and coworkers have shown that Lp(a) is eliminated through the B/E receptors like LDL, but with a significantly lower rate (15). There is no correlation to be demonstrated between Lp(a) level and LDL concentration in several population studies. This fact contributes to the finding that Lp(a) is differently synthesized from LDL. Considering the tight structural connection between Lp(a) and plasminogen, a physiological antiplasmin effect of Lp(a) may exist.

The possible role of LP(a) in atherosclerosis

Exciting studies are running concerning the mechanism of the atherogeneity of lipoprotein(a). The striking homology with plasminogen domains suggests that LP(a) is the first sure connecting bridge between the lipoproteins and coagulation system in the atherogenic process. The direct inhibitory effect of purified LP(a) on the fibrinolytic activity of human plasma with low Lp(a) concentration was demonstrated at first by us (12). Edelberg and coworkers clarify the precise mechanism of the action of Lp(a) on the formation of streptokinase-plasminogen complex presenting an uncompetitive and competitive inhibitory effect (5). The streptokinase as an external plasminogen activator is widely used for the prevention of acute myocardial infarction in patients with coronary heart disease showing hyperacute signs of thrombotic coronary occlusion. This therapy is succesful only in a part of these patients (about 40–60%, depending on different factors as for example the time of beginning of therapy etc.). The high Lp(a) concentration very likely influences the effectiveness of strep-
tokinase therapy in some patients and probably in those, in whom the therapy is unsuccessful. Gonzales-Gronow and coworkers have shown an other way of the action of Lp(a) against fibrinolysis. They have demonstrated that Lp(a) with the kringle IV domain binds to plasmin receptors of macrophages, the role of which is to protect plasmin molecules from physiological antiplasmin effects (8). This protection can be exhibited by native kringle IV as well, but the hole Lp(a) was 100 to 300 times more potent inhibitor. In general, Lp(a) inhibits the cell-surface fibrinolytic activity and to this effect the hole Lp(a) complex is needed (11).

The other mechanism of atherogenicity may be the tight binding of Lp(a) to glucoseaminoglycans. Bihari-Varga and coworkers have shown a 3.4 fold higher binding capacity to proteoglycans of Lp(a) as compared to that of LDL (4). Neuraminidase treatment of Lp(a) did not change the binding capacity for GAG. Removing the apoprotein(a) moiety of Lp(a) by using reducing agents, the binding affinity decreased by about 45%.

Several investigators have shown the presence of Lp(a) in the atherosclerotic wall (11). Thus, may be that the atherogenic action of Lp(a) is a complex process. As first, at a high Lp(a) concentration the Lp(a) accumulates in the intima of arteries through the binding to glucoseaminoglycans. The second step is a direct, locally inhibition of the continuous fibrinolytic activity with the above mentioned mechanisms.

The genetically controlled Lp(a) concentration and its possible changes

The lipoprotein(a) level is under strong genetic control. Uttermann analysed at first the relationship between the genetically determined apoprotein(a) phenotypes and Lp(a) concentra-

Fig. 3 SDS-polyacrylamide (3.75%) gelelectrophoresis of two patients with high Lp(a) level before and after fenofibrate treatment followed by western blotting and detected by polyclonal anti-Lp(a) antibody.
Lane 1: patient A before treatment
Lane 2: patient A after treatment
Lane 3: patient B before treatment
Lane 4: patient B after treatment
There is no change in Lp(a) phenotype after fenofibrate treatment in two patients with high Lp(a) level.
tions (22). He reported that apoprotein(a) is encoded by a single locus with multiple alleles, many of which produce proteins of different size. He found a significant correlation between Lp(a) phenotypes and serum concentrations. This phenotypes do not change during life.

Metabolic states showing elevated Lp(a) concentrations are under intensive investigation. After birth the Lp(a) level rises rapidly and reaches that level, which is characteristic of any individual (21). Widely used antilipidemic drugs as fibrac acid derivatives or HMG-CoA reductase inhibitors do not affect the stable Lp(a) level and the Lp(a) phenotype (Fig. 3). Only a combination of neomycin and nicotinic acid was able to decrease the Lp(a) concentration (10). Unfortunately, this combination cannot be used in the clinical practice because of its toxic side effects.

Parra and coworkers found an elevated Lp(a) serum level in patients suffering from renal insufficiency and treated chronically by hemodialysis (19). Studing patients with diffuse renal diseases and heavy proteinuria but with normal renal function we found elevated serum Lp(a) concentrations compared to age and sex matched controls (13). These findings both suggest the possible regulatory role of kidney in the Lp(a) metabolism. Further research is needed to clarify this mechanism in detail.

A lot of open questions need intensive investigations for the better understanding of the atherogonic role of Lp(a). One of the most unclear questions is whether Lp(a) causes atherosclerosis in normolipidemic patients? What is the threshold level that can promote atherosclerosis? Whether an effective anti-Lp(a) therapy may protect against atherosclerosis? These questions will be answered by the intensive worldwide running studies and contribute our efforts to decrease the mortality and morbidity of atherosclerotic vascular disease.

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