

Variation of Lp(a) Plasma Concentrations in Health and Disease

R. Siekmeier^{*1}, H. Scharnagl², G.M. Kostner³, T. Grammer⁴, T. Stojakovic² and W. März⁴

¹Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Kurt-Georg-Kiesinger-Allee 3, Bonn, Deutschland, Germany

²Klinisches Institut für Medizinische und Chemische Labordiagnostik, Medizinische Universität Graz, Graz, Österreich, Austria

³Institut für Medizinische Biochemie und Medizinische Molekularbiologie, Medizinische Universität Graz, Graz, Österreich, Austria

⁴Synlab – Medizinisches Versorgungszentrum für Labordiagnostik, Heidelberg, Eppelheim, Deutschland, Germany

Abstract: Lipoprotein(a) (Lp(a)) is an established risk marker of cardiovascular diseases which is independent from other risk markers. The main difference of Lp(a) compared to low density lipoprotein (LDL) is the apo(a) residue which is covalently bound to apoB. Apo(a) is a glycoprotein which underlies a large genetic polymorphism. The latter is caused by a variation of the kringle-IV-type-2 repeats of the protein which is characterized by a large structural homology to plasminogen. The Lp(a) plasma concentration in the population is highly skewed and determined to more than 90 % by genetic factors. In healthy subjects the Lp(a)-concentration is correlated to its synthesis and not to its metabolism. However, plasma concentrations of Lp(a) are also affected by different diseases (e.g. diseases of liver and kidney), hormonal factors (e.g. sexual steroids, glucocorticoids, thyroid hormones), individual and environmental factors (e.g. age, cigarette smoking) as well as pharmaceuticals (e.g. derivatives of nicotinic acid) and therapeutic procedures (lipid apheresis). Aim of this review was to describe the physiological regulation of Lp(a) as well as factors influencing its plasma concentration.

Keywords: Lipoprotein (a), plasma lipoproteins, atherosclerosis, coronary heart disease.

INTRODUCTION

Lipoprotein (a) (Lp(a)), for the first time described in 1963 by Berg belongs to the lipoproteins with the strongest atherogenic effect [1, 2]. Its importance for the development of various atherosclerotic vasculopathies (coronary heart disease, ischemic stroke, peripheral vasculopathy, abdominal aneurysm), however, was recognized considerably later [3-6]. With regard to its structure, Lp(a) is a low density lipoprotein (LDL), to whose apolipoprotein B (apoB) another protein, i. e. apolipoprotein(a) (apo(a)), is covalently bound by a disulfide-bridge [7]. The physiological function of Lp(a) is unknown to date, since test persons with very low or not detectable Lp(a) plasma concentrations do not present a specific phenotype. Vice versa, however, numerous studies have shown that elevated Lp(a) plasma concentrations are associated with an increased risk of atherosclerotic diseases (coronary heart disease, peripheral arterial occlusive disease, cerebral stroke) [6-11]. Apo(a) synthesis is performed in the liver, probably followed by extracellular assembly to the apoB location of the LDL [12]. The biological half life of Lp(a) is known by kinetic investigations and exceeds the half life of LDL [13, 14]. However, only little is known about the

details of Lp(a) catabolism. It is assumed that the kidney has a specific function in Lp(a) catabolism, since nephrotic syndrome and terminal kidney failure are associated with an elevation of the Lp(a) plasma concentration [15, 16]. One consequence of the poor knowledge of the metabolic path of Lp(a) is the fact that so far pharmaceutical science has failed to develop drugs that are able to reduce elevated Lp(a) plasma concentrations to the desired extent.

STRUCTURE OF LP(a)

Lp(a) is a complex particle which mainly consists of a part that is similar to LDL, to whose apoB glycoprotein apo(a) is covalently bound. To a small extent, however, apo(a) could also be detected bound to triglyceride-rich lipoproteins (Very Low Density Lipoproteins; VLDL). Corresponding to the structural similarity to LDL, both particles are very similar to each other with regard to their composition [13]. Apo(a) shows a distinct structural homology to plasminogen, whose gene is also localised on chromosome 6 [17, 18]. The kringle repeats present a particularly characteristic structure, which have a high similarity to kringle IV (K IV) of plasminogen. Additionally, apo(a) presents a kringle V structure of plasminogen and also a protease domain, which cannot be activated, as opposed to the one of plasminogen [2, 17, 18] (Fig. 1). At least 30 genetically determined apo(a) isoforms were identified in man, which are the basis for the marked

*Address correspondence to this author at the Bundesinstitut für Arzneimittel und Medizinprodukte, (BfArM), Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Germany; Tel: 0049/228-207-5360; Fax: 0049/228-207-5300; E-mail: r.siekmeier@bfarm.de

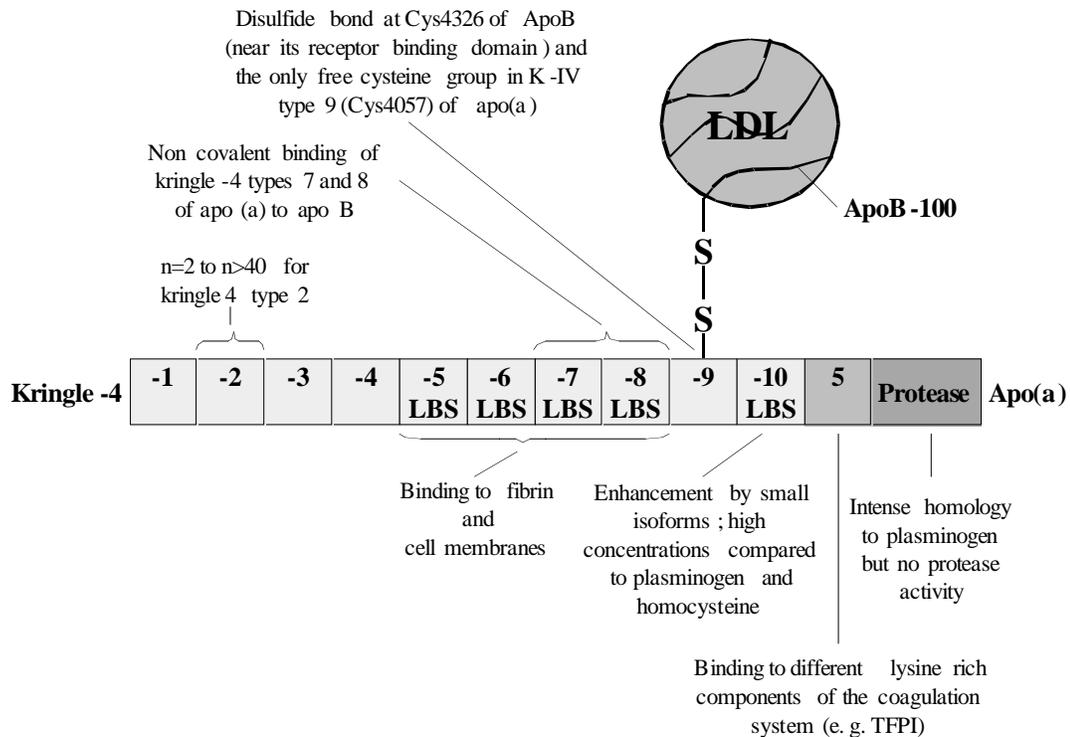


Fig. (1). Structure of Lp(a).

heterogeneity of the molecular size. The individual apo(a) isoforms differ by the number of K IV units in the molecule, i. e. corresponding to a molecular weight of approximately 12.5 kDa per K IV-unit [2, 17]. The smallest apo(a) isoform consists of one protease domain, one K V-unit and 11 K IV-units, while the apo(a) isoform of the highest molecular weight has 52 K IV-units. Between the individual K IV-units there are highly glycosylated connection units which are responsible for the high share of glycoproteins in the whole molecule [2].

LP(a) METABOLISM

Apo(a) is synthesized at least predominantly in the liver. After its synthesis it binds with high affinity to the apoB binding site of LDL. Probably, the binding is completed on the hepato-cellular surface *via* a disulfide-bridge of the Cys4326 of apoB and the only free cysteine group in K IV type 9 (Cys4057) of apo(a) [2, 19]. The synthesis of Lp(a), which thus occurs as part of an assembly, is a two-step process [20]. In a first step, which can be competitively inhibited by lysine analogues, the free sulfhydryl groups of apo(a) and apoB are brought close together. The binding of apo(a) then occurs near the apoB domain which binds to the LDL receptor, resulting in a reduced affinity of Lp(a) to the LDL-receptor. Particles that show a reduced affinity to the LDL receptor, such as particles containing apoB-48 and VLDL, are not able to form stable compounds with apo(a) [2]. Thus the largest part of apo(a) is present as apo(a) bound to LDL. Only a small, quantitatively variable part of apo(a) remains as free apo(a) and probably plays an important role in the metabolism and physiological function of Lp(a) [2, 21]. The synthesis rate of Lp(a) is strongly related to its plasma concentration and therefore depends on the apo(a)

isoform that determines plasma concentration, while the catabolism rate is only of little significance [14].

The metabolic path of the synthesised Lp(a) is largely not yet understood. Due to the structural similarity of LDL and Lp(a) it was first assumed that Lp(a), like other apo B containing lipoproteins, is degraded *via* the LDL-receptor. Thus it could be shown in *in vitro* experiments that the binding of Lp(a) to fibroblasts could be competitively inhibited by addition of LDL, but compared to LDL, Lp(a) only had a small affinity to the LDL receptor. Animal experiments (rat, rabbit, hedgehog) showed that the liver plays an important role in Lp(a) metabolism – followed by kidney and spleen [13]. On the other hand, kinetic investigations performed in man, which demonstrated a longer plasma half life for Lp(a) compared to LDL, allowed the conclusion that the LDL receptor practically has no function in the metabolism of Lp(a). Thus the fractional catabolic rates for LDL and Lp(a) are 0.38 and 0.26, respectively, in normal persons and are practically the same as for homozygotic patients with a defect on the LDL receptor (0.205 and 0.210, respectively) [13, 14]. This phenomenon was the reason that other metabolic paths are now being discussed for Lp(a). Apo(a) obviously separates from apoB in the blood and as a consequence it comes to a subsequent fragmentation into degradation products of different molecular weight induced by metalloproteinases [2, 22]. As could be shown in experiments in transgenic mice, the resulting degradation products are removed from circulation by different organs and tissues, and only a very small part of them (less than 1 % of Lp(a)) is excreted with the urine [2, 22, 23]. Other, receptor-dependent metabolic paths are assumed for the Lp(a) metabolism. Among them are LDL-receptor related protein, megalin, the VLDL

receptor and the galactose-specific asialoglycoprotein receptor (ASGPR) [2, 24].

GENETICS AND PLASMA CONCENTRATION

The plasma concentration of Lp(a) is highly skewed with regard to its frequency, whereby the concentrations among different individuals may differ by factor 1000 [13, 25, 26]. The white population shows a median of the Lp(a) concentration of approximately 8 mg/dL to 10 mg/dL, while the mean values are at an approximate level of 16 mg/dL to 18 mg/dL [13, 27]. In contrast, plasma concentrations in Black Africans are twice as high as in Caucasians, while those of Asian individuals are distinctly below that value. However, the underlying causes of these differences are not finally identified [2]. The concentrations are strictly determined by genetic factors, i. e. to an extent of 90 % to 95 %, and are subject to only low variations during lifetime [13, 28]. In detail, a total of 50 % of the plasma concentration is determined by the respective number of kringle-IV-domains, while approximately 45 % of the genetic variation of the plasma concentrations are attributable to polymorphisms and mutations of the promoter region (pentanucleotide repeat, TTTTA), to the coding regions (+93 C/T polymorphism) and to other variations of the apo(a) gene [2, 13]. Despite this Lp(a) plasma concentrations continuously rise mainly in the first weeks after birth and also in the course of the later decades in life [2]. There is a distinct inverse correlation between the respective molecular weight of Lp(a) determined by the number of kringle-IV-domains in the apo(a) part of the lipoprotein particle and the individual plasma concentrations, respectively. Thus individuals with a high Lp(a) molecular weight show low plasma concentrations, while individuals with a low Lp(a) molecular weight present high plasma concentrations [12, 29, 30]. This can be explained by the fact that apo(a) isoforms with a high molecular weight are stronger bound and degraded in the rough endoplasmic reticulum, in the golgi apparatus and in proteasomes than apo(a) isoforms with a low molecular weight [31, 32].

PHYSIOLOGICAL FUNCTIONS OF LP(a)

Based on the results of the initial investigations by Berg [1], the opinion prevailed for many years, that individuals without detectable Lp(a) plasma concentrations (so-called Lp(a)-negative individuals) did not have any defect. But due to the increasing sensitivity of the analytical procedures used in the detection it could be shown that the plasma concentrations of these individuals were only below 25 mg/dL. Later investigations in individuals with Lp(a) plasma concentrations of <0.5 mg/dL showed a disproportionately high excretion of apo(a) fragments in the urine of these individuals [2]. Now results of further investigations allow the conclusion that apart from its significance as an important agent in the development of atherosclerosis, Lp(a) has even more physiological functions, e.g. in wound healing, angiogenesis and hemostasis [2, 17, 33, 34] (Fig. 2). However, in the meaning of a pleiotropic mechanism the favorable action mechanisms are opposed by pathogenetic mechanisms, whereby the importance of Lp(a) in atherogenesis should be particularly mentioned [8-10, 17, 33, 34].

Lp(a) in Atherosclerosis

The importance of Lp(a) in the formation and progression of atherosclerotic vascular diseases could be demonstrated in numerous animal experiments. Thus evidence was supplied that in transgenic, hyperlipidemic and Lp(a) expressing Watanabe rabbits, Lp(a) leads to enhanced atherosclerosis with development of calcifications [35-37]. Under the influence of Lp(a), the binding of Lp(a) to glycoproteins, e.g. laminin, results - *via* its apo(a)-part [38-40] - both in an increased invasion of inflammatory cells [41, 42] and in an activation of smooth vascular muscle cells with an increased formation of alkaline phosphatase and subsequent calcifications [36, 37] in the vascular wall. The inhibition of transforming growth factor- β 1 (TGF- β 1) activation is another mechanism *via* which Lp(a) contributes to the development of atherosclerotic vasculopathies. TGF- β 1 is subject to proteolytic activation by plasmin and its active form leads to an inhibition of the proliferation and migration of smooth muscle cells, which play a central role in the formation and progression of atherosclerotic vascular diseases [43-46]. If TGF- β 1 fails to be activated, e.g. due to Lp(a) accumulation in the vascular wall, it is associated with an increased proliferation and migration of the smooth vascular muscle cells and the formation of atherosclerotic lesions [43, 44, 47, 48].

In man, Lp(a) is an important risk marker which is independent of other risk markers. Its importance, partly also under consideration of the molecular weight and other genetic polymorphisms, could be demonstrated by a high number of epidemiological and clinical studies investigating the formation and progression of atherosclerosis, myocardial infarction, and stroke and also by meta-analyses [8-10, 34, 49]. The simultaneous presence of other risk markers, e.g. hypercholesterolemia, hyperfibrinogenemia or reduced HDL-cholesterol, will lead to an even stronger increase of the total risk for the occurrence of cardiovascular diseases due to Lp(a) [10, 49-51]. However, there are other studies that could not find evidence for the role of Lp(a) as a risk marker for cardiovascular diseases, e.g. the Physicians Health Study [2, 52]. Possible causes for such negative results may be performance of analyses with samples that were stored for too long and the use of insufficiently validated test kits, but also the investigation of smaller study populations, which are subject to an increased influence of the skewed distribution of the Lp(a) plasma concentration in the population (<0.1 mg/dL up to >300mg/dL) [2].

Lp(a) in Hemostasis

Due to the marked structural homology between the apo(a) part and plasminogen, which both belong to the so-called plasminogen group [18], a relationship between the coagulation system and Lp(a) was assumed quite early [53]. Lp(a) is able to competitively inhibit the binding of plasminogen to fibrinogen and fibrin, and to inhibit the fibrin-dependent activation of plasminogen to plasmin *via* the tissue plasminogen activator [53-55], whereby apo(a) isoforms of low molecular weight have a higher affinity to fibrin than apo(a) isoforms of higher molecular weight [54]. Like other compounds containing sulfhydryl groups, homocysteine enhances the binding of Lp(a) to fibrin [56]. During fibrinolysis, physiological importance of which lies

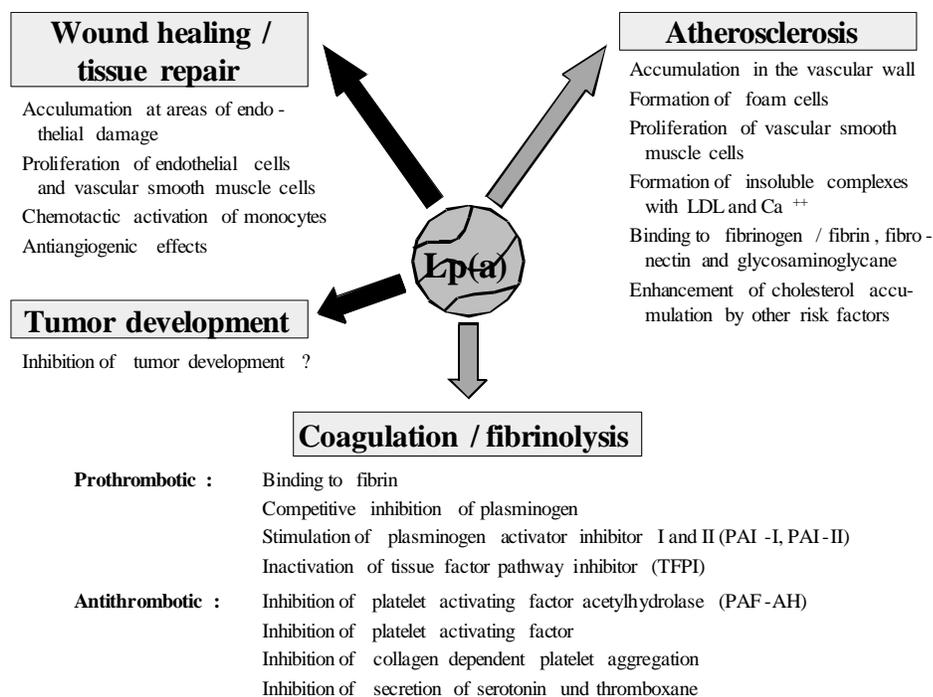


Fig. (2). Pleiotropic effect of Lp(a).

in the dissolution of fibrin deposits and in the restoration of an injured vascular endothelium [57], the binding of plasminogen to lysine residues results in plasmin activation and subsequently in the enhancement of the following fibrinolytic processes [58-63]. Lp(a) binding also involves lysine [54] with the consequence, that due to the lack of catalytic activity it comes to hypofibrinolysis and, due to the LDL-component of the Lp(a), to an accumulation of cholesterol [2, 17, 18, 33, 54, 64-66]. Moreover, Lp(a) stimulates the synthesis of plasminogen activator-inhibitor I (PAI-I) in endothelial cells or of PAI-II in monocytes [2, 67]. The thus induced decrease of plasmin activity is not only important for the fibrinolytic system, since plasmin is also required for the activation of transforming growth factor- β 1 (TGF- β 1) which plays an important role in the proliferation and migration of the smooth vascular muscle cells within the atherosclerotic process [43]. Another relationship, which also favours the formation of thromboses, between Lp(a) and the fibrinolytic system is found in its property, to bind to the tissue factor pathway inhibitor (TFPI), a regulator of the tissue factor (TF)-mediated coagulation, expressed in activated monocytes, endothelial cells and thrombocytes [33, 68-72], and to subsequently inactivate this factor [73]. But in addition to the mentioned prothrombotic properties Lp(a) also has antithrombotic properties. Thus Lp(a) binds with high affinity and specificity to the platelet activating factor acetylhydrolase. This does not only result in the inhibition of PAF, one of the strongest trigger factors of thrombocyte aggregation, but also in the hydrolysis of the short-chain phospholipids that develop during the process of lipid oxidation [2, 74-76]. Additionally, Lp(a) also leads to the inhibition of the collagen-induced thrombocyte aggregation and to the inhibition of serotonin and thromboxane secretion [2, 77]. In summary it shows that *via* various mechanisms

Lp(a) possesses both prothrombotic and antithrombotic properties, which may be an explanation for the contradictory trial results achieved in different patient cohorts, since the properties of Lp(a) find different expression [2].

Several studies demonstrate a role of Lp(a) as an important risk marker, partly independent of other risk markers, for the occurrence of an acute coronary syndrome and spontaneous, partly recurring, ischemic strokes and of venous thromboses and thromboembolism in children and adults [33, 78-84], while other investigations did not establish any relationship between the occurrence of thrombotic events or thromboembolism and the existence of an elevated Lp(a) plasma concentration [85-87]. Moreover, elevated Lp(a) plasma concentrations were measured in a number of studies performed in patients with early-stage or terminal kidney diseases and autoimmune diseases (antiphospholipid syndrome, systemic sclerosis, chronic thromboembolic pulmonary hypertension, rheumatoid arthritis and systemic lupus erythematosus), which fact supports the involvement of Lp(a) in the increased occurrence of thromboembolic events [88-97].

Lp(a) in Angiogenesis

Lp(a) is also important for the process of angiogenesis and the sprouting of new vessels. This is based on the fact that angiogenesis starts with the remodelling of matrix proteins and the activation of matrix metalloproteinases (MMP). The latter ones are usually synthesised as inactive zymogens and require activation by proteases, this is also accomplished by plasminogen. The marked structural homology of Lp(a) to plasminogen, with a simultaneous lack

of protease activity, may indicate that Lp(a) has an antiangiogenic effect [2, 98]. Accordingly, an antiangiogenic and metastasis inhibiting effect of Lp(a) and apo(a) and its fragments could be demonstrated in mice and *in vitro* [98-105].

Finally it should be stated that elevated Lp(a) plasma concentrations are found in individuals over eighty years and in tumor patients, as opposed to healthy individuals. These increases indicate that individuals with higher Lp(a) concentrations, provided they do not develop atherosclerosis, may have a certain protection against tumor diseases or that Lp(a) may have a certain function in tumor defence [2, 106]. Likewise, the plasminogen fragments have an antiangiogenic effect due to their homologous structure [106]. In summary it can be said, however, that the possible relationships between an antiangiogenic effect of Lp(a) and a possible protection against tumor formation are only insufficiently known and require extensive further experimental investigation.

INFLUENCE OF CERTAIN DISEASES ON LP(a) PLASMA CONCENTRATION

A number of different diseases (e.g. liver diseases, kidney diseases and acute phase response) hormones (thyroid hormones, androgens and estrogens) life style factors (e.g. nutrition, sports and cigarette smoking) as well therapeutic interventions (e.g. nicotinic acid, fibrates, lipid apheresis) are affecting the plasma concentration of Lp(a). However, these effects are very complex and often strongly depend on type and severity of the disease as well as type and dose of the administered pharmaceutical. A number of these factors are discussed in the following in more detail.

Liver Diseases

Cholestatic liver diseases especially those with strongly elevated plasma concentrations of lipoprotein-X are typically correlated with lower plasma concentrations of Lp(a). It is discussed that this is caused by a lack of LDL in plasma followed by an impaired assembly of LDL and apo(a) [2]. For example, Gregory *et al.* observed decreased Lp(a) plasma concentrations in patients with primary biliary cirrhosis (PBC) and other liver diseases [107]. A decrease of Lp(a) plasma concentration was also observed in patients with different acute or chronic viral liver infections as well as liver failure [108, 109] and liver cirrhosis [110]. Conflicting data are published for patients with hepatocellular carcinoma who showed decreased [111, 112] as well as increased [111, 113] plasma concentrations of this lipoprotein. In another study Koruk *et al.* found no difference of Lp(a) plasma concentrations in patients with non-alcoholic steatohepatitis compared to healthy individuals [114]. Finally, it should be mentioned that no Lp(a) can be detected in patients with paroxysmal diseases. It is suggested that this is caused by a lack of apo(a) secretion [115].

Kidney Diseases

The effect of various renal diseases on plasma concentrations and metabolism of lipoproteins including Lp(a) was subject of a large number of studies. Increased plasma concentrations of Lp(a) were observed in patients

with diabetic microalbuminuria [10, 116, 117], nephrotic syndrome [10, 93, 97, 118-120], nephropathy [10, 117] and different type and stage of kidney failure [10, 92, 93, 95, 96, 110, 121-127]. These observations suggest that Lp(a) plays a crucial role for the development of cardiovascular diseases in patients with kidney diseases. However, the results of these studies are conflicting in respect to the role of the genetically determined molecular weight of apo(a) [10, 92, 121-123, 124, 127-131].

Acute Phase Reactions

Due to the regulation of its synthesis by interleukin 6 (IL-6) Lp(a) in some respect is an acute phase protein. In consequence, inflammatory stimuli are able to affect the Lp(a) plasma concentration [126, 132]. Increased concentrations in different extent were found in chronic diseases as rheumatoid arthritis [133] or kidney disease [127], drug induced acute phase response (e.g. bisphosphonates [134]) and acute diseases as myocardial infarction or cardiovascular bypass surgery [135-139] but not after strong physical exercise [140]. However, in cases of severe inflammation due to sepsis or burn a decrease of Lp(a) plasma concentration was observed indicating a role of additional regulatory factors in critically ill patients [141].

Hormones

Different hormones affect the plasma concentration of Lp(a). This effect is independent from the effects on the other lipoproteins and in some cases it can be oppositional. In addition, even synthetic hormones can cause a variation of the Lp(a) plasma concentration. The hormonal effects of some natural or synthetic hormones as well as hormonal deprivation are described below in more detail.

Thyroid Hormones

Patients suffering from hypo- or hyperthyroidism show distinct changes of lipid metabolism and corresponding changes of the different plasma lipoproteins [2, 13, 142-145]. In principle, hypothyroidism causes an increase of Lp(a) plasma concentration whereas hyperthyroidism causes a decrease of its concentration. However, the results of the studies are conflicting. For example, Dullaart *et al.* investigated patients after radical thyroidectomy due to carcinoma and found an increase of the Lp(a) plasma concentration within the hypothyroid phase [142]. Increases of Lp(a) were also observed in other hypothyroid patients compared to healthy euthyroid controls [146-148]. In one of these studies there was a correlation between the plasma concentrations of Lp(a) and the concentrations of thyroidea stimulating hormone (TSH) which serves as a marker for the intensity of hypothyroidism. [146]. On the other hand Lee *et al.* observed no increase of the Lp(a) plasma concentration in patients with manifest hypothyroidism compared to healthy controls [149]. The results obtained in patients with subclinical hypothyroidism are also conflicting. Some investigators observed increases of Lp(a) plasma concentration in these patients compared to controls [150-153] whereas others did not [148, 149]. Milionis *et al.* also determined the molecular weight of Lp(a). However, there was no effect of the molecular weight on the Lp(a) plasma concentration before treatment. Furthermore, there was no correlation between the plasma concentrations of Lp(a) and

TSH [152]. Results of studies evaluating the effect of hyperthyroidism on Lp(a) plasma concentrations are also contradictory. For example, Bruin *et al.* and Kung *et al.* as well as Erem *et al.* observed decreased plasma concentrations in patients with manifest hyperthyroidism compared to healthy euthyroid controls as well as hypothyroid patients, respectively [147, 154, 155]. In addition, Erem *et al.* observed negative correlations between the plasma concentrations of thyroxine and Lp(a) in their patients [154]. On the other hand, Lee *et al.* found no such decrease of the Lp(a) plasma concentrations in patients with manifest or subclinical hyperthyroidism [149]. In principle, the discrepant results of these studies can be explained by several theories. Firstly, the results of the patient studies might be biased by the small number of participants because the Lp(a) plasma concentrations are affected by a number of other factors (e.g. Lp(a) genotype) which were often not considered in these studies and the weight of these influence factors is higher in smaller studies than in larger ones [143, 156, 157]. Another possible explanation is the intensity of the thyroid disease. For example, subclinical hypothyroidism has only a mild effect on lipid metabolism (including Lp(a)), whereas the effect of manifest hypothyroidism is much stronger [145].

Another aspect is the effect of treatment on the plasma concentration of Lp(a). However, the results of studies investigating the effect of hormone supplementation (triiodothyronine (T3) and thyroxine (T4)) are also contradictory. For example Dullaart *et al.* observed a decrease of Lp(a) plasma concentrations in their patients after supplementation of T3 [142]. Decreases were also observed in several studies of patients with hypothyroidism caused by other diseases supplemented with T3 or T4 [144, 146-148, 158, 159]. In one of these studies the therapy induced decrease depended on the initial plasma concentration of Lp(a) and was more pronounced in patients with Lp(a) concentrations >30 mg/dl [146]. However, other investigators found no effect of hormone supplementation on Lp(a) plasma concentrations in patients with manifest hypothyroidism [157, 160, 161]. Inconsistent data were also reported in studies investigating patients with subclinical hypothyroidism. Some investigators found a decrease of Lp(a) plasma concentrations in these patients after supplementation [152, 153] whereas no such effect was observed in the majority of studies [148, 150, 160-162]. A possible explanation for the conflicting results is that not all of the patients included in these studies suffered from increased Lp(a) plasma concentrations [152, 153] and the effect of T4 supplementation is more pronounced in patients with initially stronger increased concentrations of Lp(a) [152]. Furthermore, the lack of an effect in patients with subclinical hypothyroidism compared to patients with manifest hypothyroidism underlines the difference between both dysfunctions of the thyroid gland also affecting lipid metabolism [145]. In contrast to the large number of studies investigating the effect of hormone supplementation in patients with subclinical or manifest hypothyroidism only a minor number of studies dealt with the effect of thyrostatic treatment (thyrostatic drugs or radioactive iodine) on Lp(a) plasma concentrations in patients with hyperthyroidism (e.g. patients with Basedow's disease). However, these studies observed an increase of Lp(a) plasma concentrations which

was independent from the variations found for LDL in plasma [144, 147, 155, 159].

Androgens

Experimental studies performed in transgenic mice demonstrated a regulation of the apo(a) gene by sexual steroids and a downregulation by testosterone [163]. In humans endogenous testosterone has no relevant effect on Lp(a) plasma concentration [164-168]. In contrast, administration of testosterone or other anabolic compounds affects a large number of parameters including those of atherogenesis and lipid metabolism [169-171]. For example, Lp(a) plasma concentrations decrease in males [167, 170, 172-174] and oophorectomized females [175] after administration of testosterone. The decrease is more pronounced in individuals with higher initial Lp(a) concentrations but not dependent from the Lp(a) phenotype [167]. Even other synthetic anabolics (e.g. danazol, nandrolonedecanoate, stanozolol) administered in both genders for different clinical indications (e.g. bodybuilding, endometriosis, hemodialysis, postmenopausal osteoporosis) caused changes in plasma lipoprotein patterns and a decrease of Lp(a) plasma concentration depending in some studies on the initial plasma concentrations [176-180]. Dehydroepiandrosterone (DHEA), another anabolic steroid is physiologically synthesized and metabolized *via* androstenedione into testosterone, estradiol and estrone. In males and postmenopausal females plasma concentrations of DHEA and Lp(a) are negatively correlated [181, 182]. In postmenopausal females [183] but not in males [182] administration of DHEA causes a mild decrease of Lp(a) plasma concentrations. In contrast, orchiectomy is followed by an increase of the Lp(a) plasma concentration due to the decrease of the plasma testosterone concentration [173]. Similar increases were observed in the majority of studies performed in healthy young males and males with prostate carcinoma treated with gonadotropin-releasing hormone (GnRH) agonists (e.g. buserelin, goserelin, triptorelin) or antagonists (e.g. cetrorelix) because these substances inhibit testosterone synthesis [178, 184-186]. In one of these studies the intensity of the therapeutic effect on the Lp(a) plasma concentration depended on the initial Lp(a) concentration prior to the administration of the compound [186]. Last not least, even administration of antiandrogens (e.g. finasteride, a 5 α -reductase inhibitor) is followed by an increase of the Lp(a) concentration in plasma [187].

Estrogens and Gestagens

Beside their typical effects in females estrogens and gestagens have an antiatherogenic effect which is in part based on variations of lipid metabolism including Lp(a) [188, 189]. A number of studies demonstrated that Lp(a) plasma concentrations in premenopausal females with normal menstrual cycles are not or only slightly affected by the cyclic hormonal changes [190-193]. However, stimulation with follicle stimulating hormone (FSH) in the luteal phase causes a progesterone dependent increase of the Lp(a) plasma concentration. The increase is temporary if there is no pregnancy and persists in pregnant females [191, 193]. Further studies demonstrated that even in males there is no significant correlation between plasma concentrations of estrogen and Lp(a) [164, 166, 167].

In cases of a iatrogenic menopause in premenopausal females (e.g. by surgical measures [194, 195] or chemotherapeutics [196]) an increase of Lp(a) plasma concentration was observed beside other changes of lipid metabolism. However, an administration of estrogens causes a reversion of the observed changes including those of Lp(a) [175, 194, 195, 197]. Only in a small subset of studies no changes of Lp(a) plasma concentrations were observed in oophorectomized females vs. healthy controls and oophorectomized females before and after estrogen therapy, respectively [198, 199]. Similar results were obtained even in males after orchidectomy. In the latter administration of estrogens abolished or reversed the increase of Lp(a) plasma concentration caused by the testosterone deficiency [200, 201]. On the other hand, Berglund *et al.* observed no reduction of Lp(a) plasma concentration in their study also performed in orchidectomized males [173]. However, it is likely that the contradictory results are caused by different ways of drug administration because estrogens after oral application are subject of an intensive first pass metabolism whereas estrogens given parenterally by intramuscular injection or by transdermal application are not [173, 202]. Interestingly, comparison of the therapeutic effects of estrogen and testosterone demonstrates that both hormones cause a decrease of Lp(a) plasma concentration whereas many other physiological effects are contrary. Last not least, one more aspect of hormonal regulation of Lp(a) plasma concentration in females should be noted. Individuals suffering from polycystic ovary syndrome (PCOS; formerly Stein-Leventhal syndrome) are characterized by infertility, obesity and dyslipidemia including increased plasma concentrations of Lp(a). Investigations of Velazquez *et al.* and Yilmaz *et al.* indicated that females with PCOS have elevated Lp(a) plasma concentrations which can be lowered by administration of metformin, a substance given for treatment of diabetes mellitus type 2 [203, 204].

The natural menopause is also characterized by an increase of the Lp(a) concentrations in plasma when compared to the premenopausal values [205]. Together with other changes of plasma lipid parameters this increase correlates with an increased risk for the development of atherosclerotic diseases [206, 207, 208]. Administration of sexual steroids (e.g. estrogens, estrogens combined with gestagens) in postmenopausal females (so-called hormone replacement therapy; HRT) as well as estrogen receptor modulating substances (e.g. raloxifene) cause changes in plasma lipoprotein patterns including a decrease of Lp(a). However, the results of these studies regarding the effect of estrogens differ because the pharmacological effect strongly depends on the mode of application (transcutaneous, intramuscular, oral) and consecutively on the intensity of the hepatic first pass effect [206-219]. The decrease of Lp(a) plasma concentrations due to hormonal replacement therapy was more pronounced in individuals with high initial concentrations than in those with lower ones [206, 207, 211, 218].

Antiestrogens (e.g. tamoxifen and toremifene) which are used in the therapy of postmenopausal females with breast carcinoma oppose many of the pharmacological effects of estrogens. Interestingly, administration of these compounds beside the desired therapeutic effects cause a shift in the plasma lipoprotein status towards a lower atherogenicity

including a decrease of the plasma Lp(a) concentration [217, 220-225]. However, in one of these studies an additional effect of the phenotype of apolipoprotein E (apoE) has been described [222]. In contrast, another substance used for treatment of females with breast cancer, the aromatase inhibitor letrozole, has obviously no effect on the plasma concentration of Lp(a) [226].

Other Hormones

The effect of several other hormones on Lp(a) plasma concentrations has also been investigated. For example, administration of corticotropin or its analogues (e.g. synacthene) causes a significant decrease of Lp(a) plasma concentrations in healthy individuals, patients with terminal renal failure and hemodialysis as well as individuals after kidney transplantation [2, 227-229].

Insulin has no direct effect on Lp(a) plasma concentrations [13]. Compared to healthy individuals patients with diabetes mellitus type 1 have only small changes of Lp(a) plasma concentrations. In consequence, an improved metabolic control in these patients by an optimized insulin therapy is not followed by a relevant change of Lp(a) plasma concentration [2, 13]. In contrast, patients with diabetes mellitus type 2 are characterized by significantly higher Lp(a) plasma concentrations than healthy individuals. However, it is likely that this is a secondary effect, because these patients have an impaired renal function and in consequence a lower rate of secreted apo(a) fragments in urine [2, 230].

Two other hormones, human growth hormone (HGH) and insulin-like growth factor (IGF-1), have an antagonistic effect on Lp(a) plasma concentration [2, 231]. Administration of growth hormone, e.g. in children with impaired growth and adults with HGH-deficiency, is followed by a significant increase of Lp(a) plasma concentration [2, 232-235] which is not dependent on the Lp(a) phenotype [234]. On the other hand, application of IGF-1, e.g. in animals or patients with Laron syndrome (growth hormone resistance) causes a decrease of Lp(a) plasma concentration [236, 237] which might be caused by an increased degradation of Lp(a) [237]. Furthermore, normalization of the IGF-1 plasma concentration by the HGH-receptor antagonist pegvisomant is followed by a decrease of Lp(a) plasma concentrations in acromegaly patients [238].

INFLUENCE OF NUTRITION AND LIFE-STYLE ON Lp(a) PLASMA CONCENTRATIONS

The individual life style plays an important role for the development of cardiovascular diseases. In contrast to the large number of other risk factors which cannot be modified (e.g. gender, age) the impact of life style related factors (e.g. nutrition, sports, smoking) can be modified (e.g. cessation of smoking, changes in nutrition, sports). A number of frequent life style factors and their effect on the plasma concentration of Lp(a) is described below.

Alcohol

A number of studies has investigated the effect of ethanol consumption on the plasma concentration of Lp(a). Chronic alcohol consumption causes a strong decrease of the plasma

concentration (up to 60 %) which is dose dependent and shows no dependency on the size polymorphism of Lp(a) [239-241]. Vice versa after end or even after reduction of the alcohol consumption an increase of the Lp(a) plasma concentration has been observed [242-249]. However, the mechanism causing the alcohol dependent variation of Lp(a) plasma concentration has not been elucidated. It is discussed that the insulin-like growth factor-1 (IGF-1) binding protein is involved in this regulatory process [2, 247].

Nutrition

Moderate diets have no relevant effect on the plasma concentration of Lp(a) [250]. However, an effect of nutrition on the plasma concentration of Lp(a) has been described in a number of studies. For example, trans-fatty acids, e.g. elaidic acid which is found in fritted food in a relevant concentration, causes an increase of the Lp(a) plasma concentration between 25 % and 50 % which is more pronounced in individuals with higher initial plasma concentrations [10, 251-255]. On the other hand a protective effect of unsaturated or polyunsaturated fatty acids as well as fat modified food caused by lowering of plasma Lp(a) concentration is discussed [10, 256-260].

Cigarette Smoking

Cigarette smoking is an important risk factor for the development of cardiovascular diseases and smoking dependent changes of plasma lipoprotein patterns have been described in a large number of studies [261]. A number of studies investigated the effect of cigarette smoking on Lp(a) plasma concentrations. In some of these studies lower concentrations of Lp(a) were observed in plasma of smokers compared to nonsmokers [2, 262-265]. However, in other studies no effect of smoking was found [266, 267] or smokers had even higher plasma concentrations of Lp(a) than nonsmokers [268]. In summary, the majority of results indicate that cigarette smoking causes a reduction of Lp(a) plasma concentration. However this potentially protective effect has no clinical relevance because it is opposed by a very large number of harmful effects also caused by cigarette smoking [262].

Physical Exercise and Sports

A large number of studies has described the protective effect of physical exercise and sports on the risk for the development of cardiovascular diseases. However, the results of studies investigating the effect of both parameters on the plasma concentration of Lp(a) are conflicting. Some studies demonstrated a decrease or no relevant change of plasma Lp(a) concentrations due to physical exercise and sports [140, 250, 268-273]. On the other hand, other often older studies observed a mild increase of the plasma Lp(a) concentration without further clinical relevance [267, 274-276].

THERAPEUTIC INFLUENCE ON LP(a) CONCENTRATIONS

A large number of studies has investigated the effect of various pharmacological substances and apheresis methods on Lp(a) plasma concentrations. These are described in the following in more detail insofar as they have relevance for

the control of lipid metabolism. Further compounds like sexual steroids, glucocorticoids and thyroid hormones have been discussed before.

Administration of niacin or nicotinic acid has a positive (i. e. antiatherogenic) effect on several parameters of lipid metabolism and additionally causes a significant decrease of Lp(a) plasma concentrations. In addition, treatment with nicotinic acid can be combined with the treatment by other pharmacological substances for therapy of hyperlipidemia (e.g. gemfibrozil and inhibitors of the enzyme hydroxymethylglutaryl-CoA-reductase (HMG-CoA reductase, so-called statins) [277-287] (Table 1).

Fibrates (including gemfibrozil) are another group often used for the treatment of dyslipidemia. Substances of this group cause a reduction of mRNA for Lp(a) *in vitro* [288]. However, the results of *in vivo* studies are conflicting and demonstrate only a slight therapeutic effect regarding the effect on Lp(a) [287, 289-293] (Table 1).

Table 1. Effect of Lipid Lowering Drugs on the Plasma Concentration of Lp(a)

Compound	Effect
Niacin, nicotinic acid	↓
Fibrates	(↓)
Apheresis	↓↓
Statins	Mostly none
Resins	Mostly none
Thiazolidinedione	(↓)
Fish oil, ω3- or ω6-fatty acids, olive oil, rape oil, soy oil, polyunsaturated fatty acids and partially hydrated fatty acids	Mostly none

A very effective therapeutic approach for treatment of hypercholesterolemia characterized by high plasma concentrations of low density lipoproteins (LDL) and high concentrations of Lp(a) are different techniques of lipid apheresis. However, disadvantages of these techniques are their invasive character (like dialysis) and the required frequency of treatment (at least every two weeks) causing low compliance and high therapeutic costs. A large number of apheresis techniques has been described which is based on plasma separation (Lipid filtration (DIAMED Medizintechnik GmbH); immunoadsorption (Therasorb-LDL, Miltenyi Biotec GmbH); dextran sulphate adsorption (Liposorber LA 15, Kaneka); heparin-induced extracorporeal LDL-precipitation (H.E.L.P., B. Braun Medizintechnologie GmbH) or methods performed in full blood (direct adsorption of lipoproteins (DALI[®], Fresenius Medical Care D-GmbH); adsorption on dextran sulfate (Liposorber D, Kaneka, DIAMED Medizintechnik GmbH)). All methods have been primarily developed for treatment of high plasma LDL concentrations. However, because of the large structural similarity of LDL and Lp(a) the efficiency of these methods on both lipoproteins is very similar. In detail, dependent on the treated plasma or blood volume concentrations of Lp(a) and LDL are lowered 50 % - 74 %

and >60 % at each therapy and even other hemorheological parameters (e.g. fibrinogen, viscosity) are positively influenced [294-310] (Table 1).

In contrast, statins which play a central role in the treatment of hypercholesterolemia, despite their strong effect on LDL have no relevant effect or – in some studies – cause an increase of Lp(a) plasma concentrations if they are administered alone [209, 215, 289, 311-319]. Only few studies describe a decrease of Lp(a) plasma concentrations under statin therapy [320, 321] (Table 1). The same takes place for substances inhibiting intestinal cholesterol absorption (e.g. resins) which are sometimes combined with other lipid lowering substances, especially statins, to enhance their cholesterol lowering effect [312, 320] (Table 1).

Beside these substances which have been introduced into clinical therapy since many years there are others which have been recently introduced into therapy or which are up to now under investigation [278]. An interesting group are compounds acting *via* modulation of the peroxisome proliferator activated receptor (PPAR) from which three different subtypes (α , γ and δ) have been described [278]. This pharmaceutical group includes thiazolidinediones (so-called glitazones, e.g. pioglitazone, rosiglitazone, troglitazone) introduced for oral treatment of diabetes mellitus type 2. Studies performed in these patients revealed positive effects also on plasma lipoprotein patterns including a decrease of the Lp(a) concentration [322, 323] (Table 1).

The effects of different fatty acids (e.g. fish oil, ω 3- or ω 6-fatty acids, olive oil, rape oil, soy oil, polyunsaturated fatty acids and partially hydrated fatty acids) on plasma concentrations were subject of several studies performed in very different population and patient groups. However, the results obtained in these studies are very conflicting. In some studies an increase or a decrease of Lp(a) plasma concentration was observed whereas other studies failed to show any effect [257, 258, 260, 324-328].

Some more studies investigated the effect of other compounds like carnitine [317, 329-331], coenzyme Q₁₀ [332, 333] or aspirin [334, 335] on plasma Lp(a) and also showed conflicting outcomes.

SUMMARY

Literature data demonstrate that Lp(a) plays a relevant role as a risk factor for atherosclerosis and thrombosis. However, its physiological effect is far beyond this as Lp(a) seems also to play a role in angiogenesis as well as tumor development and metastasis. Plasma concentrations of Lp(a) are genetically determined but also can be modulated by various diseases, life style factors and drugs. Our review summarizes the effects of these parameters on Lp(a) plasma concentration and demonstrates that for some of them conflicting data have been published. However, the effects of some other parameters on Lp(a) plasma concentration is more confirmed and therefore should be considered in medical diagnostics and treatment.

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