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Effects of Hormones on Lipids and Lipoproteins

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Effects of Hormones on Lipids and Lipoproteins

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Levels of plasma lipids and lipoproteins are strong predictors for the development of atherosclerotic cardiovascular disease in postmenopausal women [1]. In women, as in men, numerous factors contribute to variations in plasma lipoproteins that may affect cardiovascular disease risk. These include age, dietary components, adiposity, genetic traits, and hormonal changes. Each of these factors may operate to varying degrees in determining changes in plasma lipoprotein profiles accompanying menopause. Cross-sectional [2,3] and longitudinal studies [3-5] have suggested increases in levels of cholesterol, low density lipoproteins (LDL) and triglyceride-rich lipoproteins associated with menopause. High density lipoproteins (HDL), which are higher in women than men and are thought to contribute to relative protection of premenopausal women from cardiovascular disease, remain relatively constant in the years following menopause [6], although small, and perhaps transient reductions in the HDL₂ subfraction have been reported in relation to reduced estradiol level following menopause [4,5]. Despite these associations, it has been difficult to determine the role of endogenous hormones in influencing the plasma lipoproteins of postmenopausal women. In principle, the effects of hormone replacement should act to reverse any alterations in lipoprotein metabolism that are due to postmenopausal hormone changes. However, as reviewed below, while there may be beneficial effects on lipoproteins, hormone

treatment does not restore a premenopausal lipoprotein profile. Furthermore, it is not clear to what extent exogenous hormone-induced lipoprotein changes contribute to the reduced incidence of cardiovascular disease with hormone replacement therapy.

Major lipoproteins and metabolic pathways. (Figure 1)

Atherogenic lipoproteins:

Endogenously synthesized triglyceride is secreted, along with cholesterol and phospholipids, in the form of very low density lipoproteins (VLDL, density <1.006 g/ml). VLDL comprise an array of particles each of which contains one molecule of a high molecular weight structural protein, apoB100, and varying amounts of lipids and smaller proteins, apoEs and apoCs. The triglyceride in VLDL is hydrolyzed in peripheral tissues by the action of lipoprotein lipase, releasing VLDL surface lipids, apoEs and apoCs which may be transferred to HDL. Triglyceride-depleted VLDL remnants are returned to the liver and taken up by receptor-mediated processes which are incompletely understood. There is evidence that LDL receptors, LDL receptor-like proteins, and perhaps other uptake mechanisms are involved.

Similar pathways operate in the metabolism of exogenously derived fat which is transported in plasma in intestinally derived chylomicron particles (not shown in Figure 1). Chylomicrons have a structure similar to that of VLDL, but are generally much larger, and contain a smaller molecular weight form of apoB, designated apoB-48.

Larger VLDL and chylomicron remnants are generally cleared from plasma over the course of several hours. However, smaller VLDL particles may be metabolized more slowly and accumulate in plasma as cholesteryl ester-rich remnants. Prolonged residence of these particles in plasma may result in further

cholesterol enrichment by transfer of cholesteryl ester from HDL through the action of cholesteryl ester transfer protein. This process, in conjunction with progressive loss of triglyceride and minor protein constituents from VLDL remnants, results in the formation of intermediate density lipoproteins (IDL, density 1.006-1.019 g/ml) and ultimately in the production of LDL (density 1.019-1.063 g/ml). LDL particles retain apoB100 and cholesteryl esters as the principal protein and lipid components, respectively, and are responsible for the bulk of cholesterol transport in plasma. As is the case for VLDL, both IDL and LDL are heterogeneous, comprising multiple subpopulations differing in size, density and composition. The metabolic and possible pathologic features of certain subclasses, particularly small, dense LDL, have been reviewed elsewhere [7,8].

The major fraction of both IDL and LDL are cleared from plasma by hepatic LDL receptors which recognize both apoE and apoB100 as ligands. This process is much slower than that for remnant clearance, resulting in LDL plasma residence times of several days. Further modifications of LDL, and perhaps IDL and remnants, may occur, perhaps related in part to prolongation of their circulation in plasma, and to interaction with tissues. One such modification, lipid peroxidation, may lead to alterations in structure of apoB100 which reduce its affinity for the LDL receptor. Alternate removal mechanisms, including activation of scavenger receptors in macrophages, result in the retention of LDL in tissues. In the artery wall, this process appears to be a critical step in the initiation of atherosclerosis, which may progress when the scavenging capacity of macrophages and perhaps smooth muscle cells is exceeded, and both cellular and extracellular cholesterol deposits accumulate. Lipid oxidation products also appear to be of importance in triggering proliferation of cellular elements in the artery wall and may also lead to altered platelet function (reviewed in [9]).

Recently, another type of lipoprotein particle, Lp(a), has been recognized as an important factor in the development of atherosclerosis [10]. Lp(a) contains apoB100 complexed with another large protein, apo(a), which is highly homologous to plasminogen. Plasma concentrations of Lp(a) vary over a wide range in the general population and appear to be under strong genetic influence. Lp(a) levels have been highly correlated with coronary disease risk in epidemiologic studies, and apo(a) has been demonstrated in arterial lesions by immunochemical techniques. While the mechanisms for the involvement of Lp(a) in atherosclerosis are not known, the interaction of apo(a) with apoB-containing lipoproteins, and perhaps also with the fibrinolytic system, may be of importance.

High density lipoproteins:

HDL comprise a complex array of particles with differing lipid and protein composition and metabolic behavior [11]. Most HDL particles contain the protein apoAI, derived from both liver and intestine, and certain subpopulations also contain varying amounts of apoAII as well as apoCs and apoEs. The bulk of HDL are thought to arise from lipid-poor precursor particles secreted by both the liver and intestine which acquire additional lipids and undergo a variety of transformations during their circulation in the blood. HDL lipids are derived both from the metabolism of apoB-containing lipoproteins, as described above, and from the direct uptake of cellular lipids, in particular unesterified cholesterol. The enzyme lecithin:cholesterol acyltransferase (LCAT), activated by apoAI, converts unesterified to esterified cholesterol, and participates in the transformation of nascent HDL in a stepwise manner to a series of progressively larger particles with increasing cholesterol and apoprotein content. The smaller and denser HDL subclasses are designated HDL₃, while the larger and more buoyant are designated HDL₂. Within both HDL₂ and HDL₃, there are multiple discrete subspecies with differing content

of apoAI and apoAII as well as other constituents. Of particular note is the largest major HDL subspecies, HDL_{2b}, which contains four molecules of apoAI without apoAII. Levels of HDL_{2b} are higher in women than in men, and in both sexes, correlate with plasma concentrations of HDL cholesterol.

HDL components leave the plasma by a variety of pathways. As described above, cholesteryl ester transfer protein may mediate cholesterol movement from HDL to apoB-containing lipoproteins, particularly lipolytic remnants, in exchange for triglycerides. The acceptor particles may then be taken up by LDL or remnant receptors. A subpopulation of HDL containing apoE also may be cleared directly by such receptors. Alternately, HDL may deliver cholesterol directly to tissues, either by selective uptake of HDL lipids, or removal of intact HDL particles. The mechanisms for such uptake, and the potential involvement of HDL receptors, have not been established.

Another mechanism implicated in regulating plasma HDL levels is the activity of hepatic lipase, an enzyme present on hepatic sinusoidal endothelial cells which catalyzes the hydrolysis of HDL phospholipids and triglycerides and potentiates hepatic HDL lipid uptake. Variations of hepatic lipase activity measured in postheparin plasma have been strongly inversely correlated with levels of HDL-cholesterol. It has also been proposed that triglyceride-enriched HDL resulting from accelerated cholesterol-triglyceride exchange are catabolized and perhaps more rapidly cleared as a result of hepatic lipase activity.

The potential ability of HDL to mediate delivery of cholesterol from peripheral tissues to the liver has led to the hypothesis that HDL has an antiatherogenic effect by promoting "reverse cholesterol transport." However, a number of other factors may underlie the inverse relationship of HDL cholesterol to risk of atherosclerotic cardiovascular disease. For example, levels of HDL-cholesterol are determined in part by the efficacy of clearance of triglyceride-rich

lipoproteins and their remnants. Thus, high HDL levels may reflect lower levels or shorter plasma residence time of potentially atherogenic remnant particles. In addition, there has been recent evidence that HDL may reduce the accumulation of lipid peroxides in LDL. A direct effect of increased apoAI production in atherosclerosis prevention has been demonstrated recently in transgenic mice overexpressing the human apoAI gene [12]. This suggests that, whatever the mechanism, genetic and other factors regulating apoAI synthesis may have important antiatherogenic effects.

Effects of estrogens on plasma lipoprotein metabolism. (Figure 2)

Estrogen treatment has been shown to increase both the rate of hepatic triglyceride production and of VLDL apoB100 secretion. Walsh et al. [13] recently have reported that oral micronized estradiol at a dose of 2mg/day increased the production of apoB in large VLDL particles (of Svedberg flotation rate or S_f 60-400) to a much greater extent than smaller VLDL (S_f 20-60). Most of the additional large VLDL was cleared directly from plasma, with a smaller portion converted to smaller VLDL and LDL. In addition, there was an increased fractional catabolic rate of LDL. The latter finding is consistent with evidence from animal studies that estrogens increase the number of hepatic LDL receptors.

The net influence of estrogens on apoB-containing lipoproteins thus depends on the balance between increased production of large, triglyceride-rich VLDL and increased clearance of these particles as well as cholesterol-rich remnants and LDL.

There is little information as to the metabolic mechanisms by which estrogens influence HDL levels. In nonhuman primates, estrogen treatment has been found to increase both apoAI and apoAII production rates [14]. High-dose ethinyl estradiol treatment of premenopausal women was shown to increase

production rates of HDL apoAI in particular [15]. On the other hand, estrogen treatment results in significant suppression of hepatic lipase activity [15,16], and in a preliminary study in postmenopausal women, reduced HDL fractional clearance has been reported. Either increased apoAI production or reduced hepatic lipase activity might be expected to induce a preferential increase in HDL₂ subclasses.

Progestin effects on lipoprotein metabolism.

The common practice of using progestins to counteract estrogen-induced endometrial hyperplasia raises the question as to the effects this may have on lipoprotein metabolism. Natural progesterone, while not extensively studied, has not been found to cause significant changes in levels of plasma lipoproteins [17-20]. On the other hand, synthetic progestins, particularly those with evidence of androgenic activity (e.g., norethindrone, levonorgestrel), may have significant metabolic effects. The best documented effect of androgenic progestins on lipoprotein metabolism is increased hepatic lipase activity, which in turn has been strongly correlated with reduced levels of HDL cholesterol, particularly in the HDL₂ subclasses [16]. Androgenic progestins are also known to reduce triglyceride levels [17], although the mechanism of this effect is not understood. Some effects of these agents may also be mediated by insulin resistance, which has been associated with a dyslipidemia characterized by increased levels of VLDL and reduced levels of HDL-cholesterol [21].

Effects of hormone replacement therapy on plasma lipid and lipoprotein cholesterol levels.

A large number of cross-sectional and longitudinal studies have assessed the influence of postmenopausal hormone replacement regimens on plasma lipoprotein concentrations. These have been extensively reviewed recently [22,23].

The findings of these studies reflect a number of sources of variation, including study designs, size and characteristics of study populations, hormone formulations, treatment regimens, duration of use, and laboratory methodology.

Estrogen replacement therapy:

In general, studies of lipoprotein changes with estrogen replacement are consistent with the known effects of estrogens on lipoprotein metabolism described above. These may be summarized as follows:

1. *Plasma triglyceride and VLDL levels increase in a dose-dependent manner.* In the Lipid Research Clinics of North America Study (LRC), a comparison of 370 non-menstruating 45-64 year old women not using estrogens with 239 women using equine estrogens at varying doses demonstrated a 26% higher median triglyceride level in the estrogen users [24]. A summary analysis by Bush and Miller of ten randomized and crossover studies employing conjugated estrogens, adjusted for variables including sample size (ranging from 6 to 265) and duration of treatment (ranging from one to 12 months), revealed an overall increase in triglycerides of 20%, with levels increasing as a function of estrogen dose [25]. A similar mean increase (24%) was observed by Walsh et al. in a recent double-blind placebo controlled crossover study of 31 postmenopausal women treated with conjugated equine estrogens for three months at a dose of 0.625 mg/day, while the mean increase at 1.25 mg/day was substantially greater (38%) [13]. It should be noted that these studies were carried out in normolipidemic women. Women with primary hypertriglyceridemia may develop severe hyperlipemia on estrogen replacement therapy [26], and in such patients, estrogens should be used with caution and only after therapeutic reduction of triglyceride levels to less than 500 mg/dl.

2. *Plasma total and LDL-cholesterol levels decrease.* In the LRC Study, median LDL-cholesterol was 11% lower in equine estrogen users vs. non-users [24].

Three other large cross-sectional studies revealed similar reductions in LDL-cholesterol [27-29] with dose-response effects between ≤ 0.625 mg/day and $\geq 0.9-1.25$ mg/day reported in two of the studies [27,29]. The summary of adjusted results from ten randomized studies by Bush and Miller [25] indicated an average 6% reduction: 4% with 0.625 mg/day and 8% with 1.25 mg/day. In the recent study by Walsh et al. [13], the reductions were greater: 15% at the lower dose and 19% at the higher dose, with a nonsignificant dosage effect. Thus, the magnitude of LDL-cholesterol reduction in relation to dose of conjugated equine estrogen appears to be variable. This may be due to a variety of factors, including variations in LDL metabolism among study populations and duration of use. Furthermore, most studies used indirect rather than direct measurements of LDL-cholesterol. Since the indirect method depends on estimating VLDL cholesterol content from plasma triglyceride $\times 0.2$ [30], it is possible that significant and variable errors may be introduced by variation in lipoprotein cholesterol and triglyceride composition with estrogen use. Furthermore, while estrogen use has been reported to result in no significant changes in LDL particle size [31], it is possible that the lowering of individual LDL subclasses may differ in individuals with differing LDL subclass distributions.

3. *Plasma HDL-cholesterol levels increase, principally HDL₂.* Median HDL-cholesterol was found to be 10% higher in users of conjugated estrogens in the LRC Study [24], with similar increases observed in three other cross-sectional studies [27-29], two of which detected an apparent effect of dose [27,29]. In the ten prospective trials summarized by Bush and Miller [25], the average adjusted increase was also 10%, without an apparent dose effect. In the studies of Sherwin et al. [32] and Walsh et al. [13], increases in HDL-cholesterol were greater: 14% and 16% at 0.625 mg/day and 19% and 18% at 1.25 mg/day, suggestive of a small, but not significant dose dependence. As in a number of other studies [33,34], the increase

was restricted to the HDL₂ subclasses. Thus, as is the case with LDL-cholesterol, there may be saturation of the effects of conjugated equine estrogens at 0.625 mg/day, although there is clearly much interindividual variation in response.

4. *The lipid and lipoprotein effects of estrogens are greater with oral than with systemic administration.* A number of studies have indicated that systemic estrogen therapy, administered as percutaneous estradiol patches or creams, have little or no impact on plasma lipid and lipoprotein cholesterol levels [35-41]. Other studies, however, have detected moderate increases in levels of HDL [34,42-44] and reductions in LDL [20,44]. While there are a number of differences in experimental methodology among these studies, it has been pointed out that some differences in the findings may be related to the relatively greater plasma levels of systemically administered estrogens that are required to achieve intrahepatic hormone levels comparable to those achieved via the portal circulation after oral administration.

Combination hormone replacement therapy:

The effects of estrogen-progestin combinations on plasma lipid and lipoprotein cholesterol levels in postmenopausal women have been examined in a large number of studies employing various hormonal replacement regimens. These studies have been reviewed recently in detail [22,23]. The following represents general observations that may be drawn from an overview of these as well as some more recent studies.

1. *The metabolic effects of added progestin are related to the dose and relative androgenic potency of the hormone preparation and the concomitant dose of estrogen.* On a weight basis, the C21-hydroxyprogesterone derivatives (e.g., medroxyprogesterone and medrogestone) are less metabolically active than the 19-nortestosterone derivatives (e.g., norethindrone) and levonorgestrel [17,45,46].

While, as discussed above, progesterone is felt to be relatively inert in its effects on lipoprotein metabolism, it has been reported recently that oral micronized progesterone reversed increases in HDL cholesterol associated with percutaneous estradiol therapy, but augmented the increase in HDL and attenuated the increase in triglycerides observed with oral conjugated estrogens.

2. *Addition of progestin is associated with variable increases in levels of plasma triglyceride and VLDL beyond those seen with estrogen alone.* The increase in triglyceride tends to be blunted with the more androgenic progestins [47]. This may be related to the finding that a combination of estradiol and d,l-norgestrel results in increased fractional VLDL apoB clearance without an increase in VLDL apoB production rate [48].

3. *Estrogen-induced reductions in LDL-cholesterol are affected minimally, if at all, by addition of conventional doses of progestins [22,47].* While this effect would appear to represent minimal interference of progestins with the beneficial effects of estrogen on LDL metabolism, it has been reported that an oral estradiol-norgestrel combination decreased LDL apoB production rate without affecting fractional LDL apoB clearance [48]. This finding stands in contrast to the recent report that estrogen therapy alone reduces LDL levels primarily by increasing fractional LDL apoB catabolic rate [13]. Thus, estrogens and estrogen-progestin combinations might alter LDL levels by different mechanisms, and this might have consequences for the prediction of effects on coronary disease risk.

4. *Most progestins attenuate estrogen-induced increases in HDL-cholesterol (principally HDL₂).* While this effect has been reported to be more pronounced with high doses of 19-nortestosterone derivatives or levonorgestrel than with 21-hydroxyprogesterone derivatives, essentially complete reversal of estrogen-induced increases in HDL and HDL₂ cholesterol have been observed with endometrial

suppressive doses of cyclic medroxyprogesterone (10mg), norethindrone (1mg), and d,l-norgestrel (0.15 mg) [22,47].

Recently, medroxyprogesterone (2.5 mg) in combination with conjugated equine estrogens (0.625 mg) given as continuous therapy has been reported to increase HDL levels more than a cyclic regimen including medroxyprogesterone at a 5mg dose [49], but there has been no controlled comparison of the same regimens given with estrogen alone.

5. *Observational studies of lipid and lipoprotein levels in older users of combination hormone replacement therapy have not demonstrated the effects on HDL levels observed in short term clinical trials.* A cross-sectional study in a retirement community in California showed no differences in plasma triglyceride, LDL-cholesterol, or HDL-cholesterol levels in users of estrogen-only versus combination hormone replacement therapy [28]. Similar results have been observed recently in studies carried out in a second California retirement community [29]. In the latter study, there was also no detectable difference with doses of medroxyprogesterone ranging from 2.5 mg to 10 mg per day, administered from 5 to 25 days/month. In both studies, differences in lipid and lipoprotein levels between nonusers of hormones and estrogen-only users were comparable to those reviewed above. While multiple explanations might be offered for these results, ranging from subject self-selection to poor progestin compliance, it should also be noted that longer term prospective treatment trials (e.g., > 1 yr) have not been performed, and it is possible that progestin-induced alterations of lipoproteins (notably HDL) become attenuated over time.

Effects of hormone replacement therapy on other lipoprotein parameters that may affect cardiovascular disease risk.

A recent preliminary study has indicated that one year of therapy with cyclic conjugated equine estrogens (0.625 mg/day, 25 days/month) and medroxyprogesterone acetate (10 mg/day, 13 days/month) results in a substantial reduction of plasma levels of Lp(a). If this result is confirmed, hormone replacement therapy may be one of the most effective available methods available for lowering Lp(a) concentrations [50].

Effects of hormone replacement regimens on HDL- and HDL₂-cholesterol are generally accompanied by parallel increases in plasma apoA-I levels [34,47]. While reductions in levels of plasma apoB100 have been reported with estrogen replacement [51] and with combined estrogen-progestin therapy [52], the relative reduction may be less than that of LDL-cholesterol [52]. Recently, it has been reported that reductions in LDL-cholesterol with oral conjugated estrogens were not accompanied by reductions in LDL apoB concentration [34], suggesting a change in LDL composition to yield a cholesterol-depleted and possibly higher density LDL particle. As in previous cross-sectional studies [24], increased triglyceride content of LDL as well as other lipoprotein classes was observed with oral estrogens [34]. However, detailed studies of changes in LDL composition, or changes in potentially atherogenic components included in the LDL-cholesterol measurement, such as IDL and small, dense LDL, have not been carried out. Finally, while *in vitro* studies have indicated a potential effect of estrogens in reducing susceptibility of LDL to copper- and cellular-induced oxidation [53], it has not been established to what extent this may contribute to protection from LDL oxidation and atherosclerosis *in vivo*.

Considerations for future research.

The substantial reduction in risk of coronary artery disease associated with estrogen replacement therapy has been related in part to increased HDL-cholesterol. There is little evidence to support a consistent effect of estrogens or hormone replacement therapy on other well-established coronary disease risk factors, including blood pressure and diabetes mellitus. However, an increasing body of evidence, derived largely from animal studies and reviewed elsewhere in this volume, has supported the concept that a major portion of the benefit of estrogen therapy may result from direct effects on the arterial wall and on the atherosclerotic process which are not correlated with changes in standard plasma lipoprotein measurements. The doses of estrogen used in these studies have been relatively high, and it remains to be established whether comparable effects apply to women treated with conventional hormone replacement regimens.

Further information is required in order to gain a more thorough understanding of clinically important effects of hormone replacement therapy on lipoprotein metabolism:

1. Analyses of hormonal effects on specific factors involved in plasma lipoprotein metabolism that may be more predictive of reduced coronary disease risk than standard lipid measurements, e.g., LDL and HDL subfractions, apoproteins, Lp(a), oxidized LDL, lipid transfer proteins, LDL receptors.
2. An understanding of the basis for the observation that increased triglyceride levels are a univariate predictor of coronary disease in women, whereas reduced coronary disease risk is observed in the setting of increased triglyceride and VLDL levels induced by estrogen treatment. Possible explanations to be addressed are that smaller VLDL and IDL may be of greater pathologic importance than the larger VLDL induced by estrogen, and that clearance of potentially atherogenic VLDL and chylomicron remnant lipoproteins is enhanced by estrogen treatment.

3. Information on the long-term effects of various doses and regimens for estrogen-progestin combinations, so that guidelines may be developed to optimize lipoprotein changes that may benefit coronary disease risk.

4. Studies of the effects of hormone replacement regimens in dyslipidemic women for whom cardioprotective effects would be particularly desirable, but who may require individualized approaches to treatment.

5. Studies of the possible influence of ethnic and genetic factors that might influence lipoprotein responses to hormone replacement therapy.

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FIGURES

Figure 1. Major lipoproteins and metabolic pathways.

Figure 2. Effects of estrogens on plasma lipoprotein metabolism.

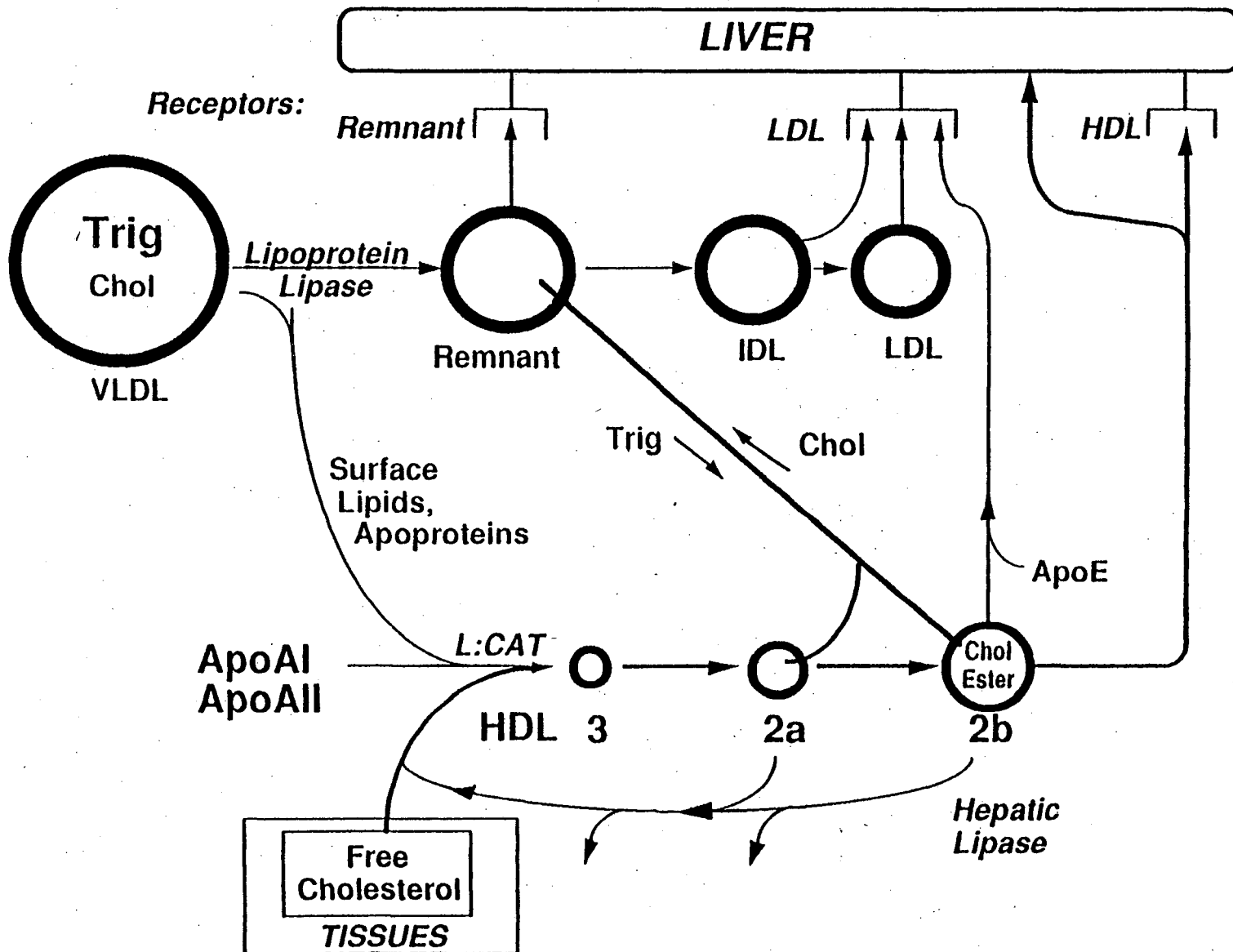


Figure 1

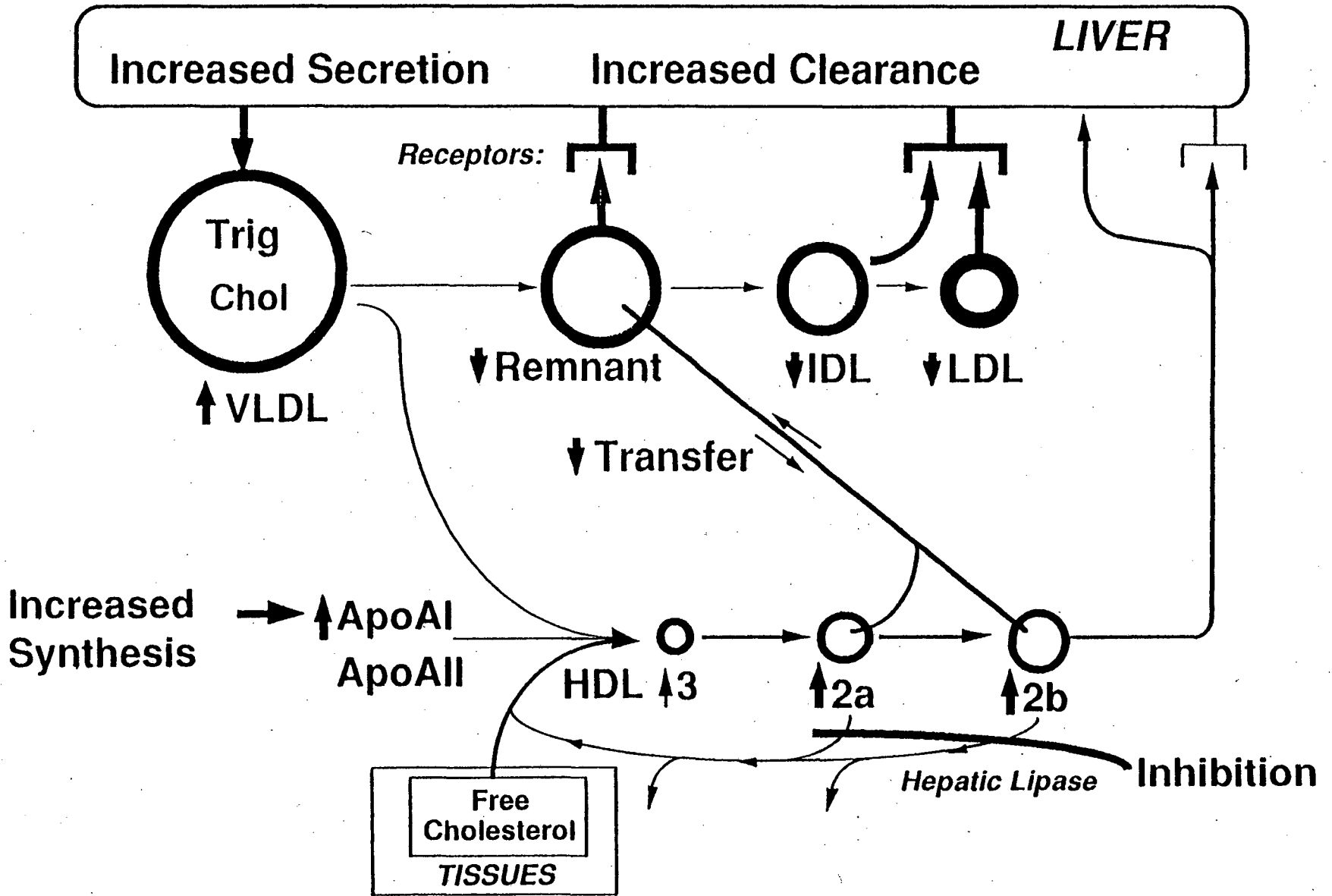


Figure 2

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