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CHAPTER 28

Liver Inclusive Protein, Lipid and Carbohydrate Metabolism

L. SAHLIN and B. VON SCHOULTZ

A. Liver – A Non-Reproductive Target Organ for Estrogens

The mammalian liver contains specific estrogen receptors (ERs) (DUFFY and DUFFY 1976; ATEN et al. 1978; ERIKSSON 1982a; ERIKSSON 1982b; FREYSCHUSS et al. 1991), but is still quite different from other target organs for estrogens. The number of binding sites in the liver is only about one-eighth to one-tenth that of the normal receptor concentration in classical target organs such as the uterus (ERIKSSON 1982a; ERIKSSON 1983). Liver receptors, in significant concentration, can only be detected after the onset of puberty and, in rats, hypophysectomy results in a major decrease of hepatic estrogen receptors (ERIKSSON 1983). Activation of the receptor is not associated with the induction of a progesterone receptor in the liver and, compared with the estradiol doses required to elicit response in the endometrium, excessively high doses are necessary to achieve similar effects in the liver (MARR et al. 1980; LAX et al. 1983). EAGON et al. (1986) have found a circadian rhythm in the hepatic ER, although we have not been able to repeat these findings (SAHLIN and FREYSCHUSS, unpublished observations).

ER dimerization enables the complex to interact with estrogen responsive elements (EREs) to activate transcription of target genes. Although phosphorylated in the resting state, a receptor bound to DNA is further phosphorylated at several serine and possibly also tyrosine residues (WASHBURN et al. 1991). Changes in phosphorylation may function to regulate ER binding to ligands, DNA or other proteins (AUCHUS and FUQUA 1994). After binding to the ERE, the genes are transcribed and mRNAs from the estrogen responsive genes are produced. This finally results in an increased synthesis of specific proteins that mediate the biological effects of true hormone stimulation (CLARK and PECK 1979). The specificity of response is controlled by the amount of receptors within a cell, as well as co-regulators, and the accessibility to target genes in the chromatin (BANIAHMAN et al. 1994).

A direct relationship between receptor concentration and the degree of biological response has been described (EVANS et al. 1987; WEBB et al. 1992), although other groups have not found any correlation using their experimental systems (GAUBERT et al. 1986; DARBRE and KING 1987). It has also been shown that the threshold level of the receptor amount for one response is quite

different from the concentration required for another response to occur (RABINDRAN et al. 1987; COOK et al. 1988; DONG et al. 1990). These results suggest that other factors, in addition to the receptor concentration, determine the biological effect of steroid hormones.

I. Regulation of the Hepatic Estrogen Receptor

Hepatic ER levels are very low, and the liver is unresponsive to estrogens in the absence of growth hormone (GH) (STEINBERG et al. 1967; NORSTEDT et al. 1981; THOMPSON et al. 1983). Therefore, the lack of hepatic response to estrogens in hypophysectomized rats may be due to loss of ERs, as well as loss of GH. This makes it difficult to discriminate between direct effects and indirect effects due to alterations in GH secretion, which are known to occur during estrogen treatment of rats (MODE and NORSTEDT 1982; PAINSON et al. 1992) and humans (DE LEO et al. 1993).

In ovariectomized rats treated with estradiol, the levels of ER and ER mRNA were significantly increased (SAHLIN et al. 1994). This effect was attenuated by dexamethasone pretreatment (SAHLIN 1995). In hypophysectomized rats GH increased both ER and ER mRNA (FREYSCHUSS et al. 1994). This effect of GH was enhanced when given together with dexamethasone. The synergy between GH and dexamethasone in the formation of the ER protein has also been shown in cultured hepatocytes (FREYSCHUSS et al. 1993). Thus, in ovariectomized rats, in which estrogen is the main regulator of ERs and ER mRNA, the effect of estradiol is attenuated by dexamethasone, whereas, in hypophysectomized rats, in which GH is the main regulator of ERs and ER mRNA, dexamethasone acts in synergy with GH.

Hepatic ERs and ER mRNA levels have been shown to decrease after thyroidectomy, compared with the levels in normal rats. GH treatment increased the ER level to half of the normal value, although ER mRNA was not affected (ERIKSSON and FREYSCHUSS 1988; FREYSCHUSS et al. 1994).

II. Exogenous Estrogens

Treatment with exogenous estrogens is known to affect several aspects of liver metabolism (ANDERSSON and KAPPAS 1982). Alterations in protein synthesis (Table 1), coagulation factors (Table 2), lipid metabolism (Table 3) and carbohydrate metabolism are of particular interest and may have important clinical implications. Changes in the synthesis of liver-derived proteins, such as angiotensinogen, high-density lipoprotein (HDL) and low-density lipoprotein (LDL), various coagulation factors and antithrombin III, may influence the risk of hypertension, hyperlipidemia, and hypercoagulability during estrogen treatment.

The effect of sex steroid hormones may be mediated principally in two ways: directly via receptor binding in target cells or indirectly by modifying the secretion of other hormones (VON SCHOULTZ and CARLSTRÖM 1989). In the liver, the given hormones are rapidly metabolized, processed and excreted

Table 1. Proteins affected by estrogen treatment

Protein	Effect
α1-Antitrypsin	+
Albumin	–
Alkaline phosphatase	+
Angiotensinogen	+
Bilirubin	+
Ceruloplasmin	+
Corticosteroid-binding globulin	+
χ-glutamyl transpeptidase	+
Growth hormone	+
Growth hormone binding protein	+
Insulin-like growth factor-I	–
Haptoglobin	–
Leucin aminopeptidase	+
α2-Macroglobulin	+
Orosomucoid	–
Pregnancy zone protein	+
Retinol binding protein	+
SHBG	+
Thyroxin-binding globulin	+
Transcortin	+
Transferrin	+

Table 2. Coagulation factors affected by estrogen treatment

Coagulation factor	Effect
Antithrombin III	–
Coagulation factor II	+
Coagulation factor VII-X	+
Coagulation factor XII	+
Complement reactive protein	+
Fibrinogen	+
Plasminogen	+
Protein C	+
Prothrombin time	–

Table 3. Lipids affected by estrogen treatment

Lipids	Effect
Apolipoprotein-A	+
HDL	+
LDL	–
Lecithin	+
Total lipids	+
Triglycerides	+

HDL, high-density lipoprotein; *LDL*, low-density lipoprotein

mostly as sulfo- or glucuroconjugates. The interaction between exogenous sex steroids and the endogenous substances that are normally metabolized in the liver contributes a further stress to hepatic cells. It seems that only synthetic estrogens or high doses of natural estrogens, given orally, will saturate the hepatic metabolic capacity and cause a pharmacological response (STEINGOLD et al. 1986; MARR et al. 1980).

The impact of exogenous estrogens on liver metabolism is mainly dependent on two factors: the route of administration and the type and dose of estrogen (Fig. 1).

Oral treatment with estrogen pills is simple and convenient and has a well-documented therapeutic efficacy, but is also, in many ways, non-physiological (HOLST 1983; JUDD 1987). In the intestinal wall, about 70% of the ingested estradiol is metabolized to estrone, which has an approximate biological activity of about one-third that of estradiol (LYRENÄS et al. 1981). The intestinal absorption is rapid and yields high concentrations of hormone in the portal circulation. Very high concentrations are needed to saturate the hepato-digestive defense mechanisms before a general therapeutic effect can be achieved. Thus, it is necessary to use roughly a 20-fold higher dose via the oral route than parenterally. In fact, transdermal administration of 50–100 μg of estradiol provides the same therapeutic effect in postmenopausal women as 2 mg of estradiol given orally.

Available data imply that the multitude of effects following oral administration of high doses of synthetic estrogens to a major extent reflect a phar-

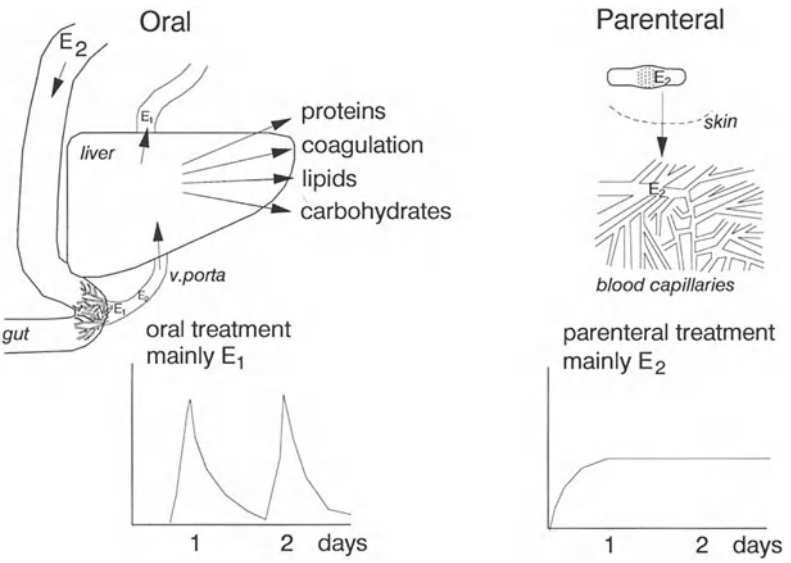

Fig. 1. There are distinct differences in the metabolism and action of estrogen according to the route of administration

macological rather than a physiological influence on liver metabolism. Specific differences in hepatic action between the native hormone estradiol-17β and synthetic estrogens have been clearly demonstrated (Steingold et al. 1986). This concept has stimulated work on alternative non-oral delivery systems (Holst 1983; Judd 1987), and in developing derivatives of natural estrogens lacking the hepatic side effects (Elger et al. 1995). Numerous clinical and animal studies have demonstrated that the hepatic impact of estrogen treatment can be reduced dramatically by modification of the type of estrogen and the route of administration (Elkik et al. 1982; Holst 1983; Fåhreus and Wallentin 1983; Judd 1987; de Ligueires and Basdevant 1987; Stege et al. 1987; Elger et al. 1995).

Indeed, when the native estrogens are given parenterally, the effects on liver-derived plasma proteins, coagulation factors, lipoproteins and triglycerides are very weak or completely abolished (Judd 1987; de Ligueires and Basdevant 1987; Stege et al. 1987; Elkik et al. 1982; Fåhreus and Wallentin 1983; Holst et al. 1983). In a rat model, the estradiol-17β-sulfamate has proven to have a 90-fold elevated systemic effect, compared with estradiol-17β, when given orally, combined with a reduction of hepatic estrogenicity (Elger et al. 1995). Systemic estrogenicity was quantitated by assessment of uterine weight, vaginal cornification and measurement of gonadotropins (Elger et al. 1995). This substance may allow the use of native estrogens orally without affecting hepatic metabolism.

Estriol, given in low, daily doses, appears to be quite inert in stimulating the hepatic "estrogen-inducible" proteins, plasma renin activity and coagulation factors, as well as in modifying total cholesterol, HDL-cholesterol and triglycerides (Errkola et al. 1978; Bergink et al. 1981; Campagnoli et al. 1981).

B. Plasma Proteins

Estrogen treatment affects the synthesis of several proteins in the liver (Table 1), some of which are potentially important in development of disease or protection against disease (Laurell and Rannevik 1979; von Schoultz et al. 1989; L'Hermite 1990). Oral therapy increases the serum concentrations of several proteins in a dose-dependent way (von Schoultz 1988). When treatment is started, the serum concentration of the respective protein increases. After about 1–3 months, they have reached new values which remain stable for the rest of the treatment period (von Schoultz 1988). This serum protein induction is reversed by androgens and progestogens, particularly the 19-nor steroids. The net change in protein level may be used as an index of "estrogenicity" for different estrogen/progestogen combinations in clinical practice. Whether synthesis of these proteins is directly regulated by estrogens, or indirectly through alterations in secretion of other hormones, especially GH, has not yet been resolved (von Schoultz and Carlström 1989). With regard to

some of the estrogen-induced proteins, such as angiotensinogen and hepatic LDL receptor, the effects of estrogens are probably direct, at least partly, while other proteins may be regulated solely indirectly through other factors affected by estrogens, for instance GH secretion (CARLSSON-BOUSTEDT et al. 1987).

The regulation of protein metabolism can be achieved both at a transcriptional and translational level. In Xenopus liver cells, estrogen increases the half-life of vitellogenin mRNA from 16 h to 3 weeks (BROCK and SHAPIRO 1983; NEILSON and SHAPIRO 1990), resulting in a massive increase of vitellogenin mRNA. In contrast, estrogens destabilize the albumin mRNA in the same cells (KAZMAIER et al. 1985; WOLFFE et al. 1985). An estrogen-inducible ribonuclease activity has been identified in Xenopus liver (PASTORI et al. 1991) which may mediate hormone regulating changes in mRNA stability in this tissue.

An increase in blood pressure is known to occur in some women during hormonal contraception and, also, but less frequently, during hormonal replacement therapy. While the physiological effect of estrogen is to promote blood flow and vasodilatation and rather to reduce blood pressure, the pharmacological action of exogenous estrogen on liver protein synthesis may cause an opposite effect. The influence on angiotensinogen is of particular interest in this respect. Estrogen treatment increases the synthesis/secretion of angiotensinogen in adult rat and human livers (KRAKOFF and EISENFELD 1977; VON SCHOULTZ et al. 1989). A dose-dependent response in the range 50–300 μg ethinylestradiol/day/rat has been shown (HONG-BROWN and DESCHEPPER 1993). Most data indicate a direct stimulatory effect of estrogens on the synthesis of angiotensinogen in the liver. Oral estrogens are stronger stimulators than parenterally administered ones (DUPONT et al. 1991), and angiotensinogen secretion is increased by estrogen in isolated perfused livers (NASJLETTI and MASSO 1972). There is no response to estrogens with respect to angiotensinogen in livers of hypophysectomized or immature rats where hepatic ER levels are low (KRAKOFF and EISENFELD 1977; EISENFELD and ATEN 1980). An ER-negative hepatoma cell line, unresponsive to estrogens, was stably transfected with functional ERs. Thereafter, estrogen treatment resulted in increased angiotensinogen secretion (KLETT et al. 1992).

Elements conferring an estrogenic response have been identified in the promoter region of the angiotensinogen gene (FELDMER et al. 1991). Although even the relatively low doses of orally administered estrogens used in postmenopausal treatment today may increase circulating angiotensinogen levels, this does not seem to increase blood pressure (DUPONT et al. 1991). Thus, the physiological/pathological importance of this phenomenon is not known, and the importance of estrogens in regulation of blood pressure is unresolved (L'HERMITE 1990). In a recent paper WANG et al. (1995) have shown that physiological (endogenous) levels of estrogen do not affect or control angiotensinogen synthesis.

Circulating insulin-like growth factor-I (IGF-I) levels are reduced by oral estrogen therapy and this decrease has been proposed to result in the increased GH secretion due to reduced feedback inhibition by IGF-I (Kelly et al. 1993).

The antiestrogen tamoxifen, when given to subjects with estrogen deficiency, has mild estrogenic properties on protein metabolism (Helgason et al. 1982). When added during estrogen therapy, it strongly counteracts the therapeutic effects of the estrogen. The estrogen-sensitive liver-derived pregnancy zone protein (PZP) showed the most pronounced reduction after three cycles of tamoxifen addition, whereas sex hormone-binding globulin (SHBG) levels were only moderately reduced (Ottosson 1984). Raloxifene lowered alkaline phosphatase in a short-term study in postmenopausal women (Draper et al. 1996). Progestogens are known to elicit antiestrogenic effects on protein metabolism (von Schoultz 1988).

I. Coagulation Factors

Estrogens influence liver-derived coagulation factors in a dose-dependent manner (Table 2). Estrogens used in the treatment of prostatic cancer and in oral contraceptives have been shown to increase the risk of thrombo-embolic diseases (Meade 1981; Henriksson et al. 1986). The risk has been related to high doses of orally administered synthetic estrogens, especially ethinylestradiol, but recently, the use of estradiol or conjugated equine estrogens for hormonal replacement therapy has also been associated with an increased incidence of thrombo-embolic disorders (Wren 1988; Daly et al. 1996). The exact mechanisms involved have not been fully elucidated, but include an increased synthesis of some coagulation factors and decreased synthesis of antithrombin III in the liver (Henriksson et al. 1986). A possible direct activation of the coagulation system by estrogens has also been suggested, but is probably of less importance (Inauen et al. 1991). The choice of the corresponding progestogen affects serum levels of some clotting factors, but the possible risk of thrombosis has not been shown convincingly (Kuhl 1996). Parenteral administration of estrogens used for contraception or postmenopausal estrogen therapy seems to have less influence on the coagulation system, and it is unclear to what extent such therapy will increase the risk for thrombo-embolic disease (Devor et al. 1992). As for plasma proteins, the estrogenic effects on certain coagulation factors, in particular factors II, VII and protein C, are counteracted by androgens and 19-nor steroid progestogens (Kuhl 1996).

Oral tamoxifen citrate treatment induced a modest decrease in anticoagulant proteins, but without biochemical signs of activation of coagulation and fibrinolysis (Mannucci et al. 1996). Tamoxifen has been shown to decrease fibrinogen levels, after both 2 years and 5 years of treatment (Love et al. 1994; Grey et al. 1995).

C. Lipids

Effects seen on lipid levels after oral estrogen therapy are summarized in Table 3. The LDL receptor is important in the regulation of serum cholesterol and is responsible for removal of most of the circulating cholesterol (RUDLING 1987). A 3-fold induction of hepatic LDL receptor levels has been reported in prostatic cancer patients receiving pharmacological doses of estrogens (ANGELIN et al. 1992). After treatment of rats with high doses of estradiol or ethinylestradiol a 5- to 10-fold induction of hepatic LDL receptor levels is observed, which is accompanied by drastically reduced serum cholesterol levels (KOVANEN et al. 1979; SRIVASTAVA et al. 1993). This effect of estrogens is observed neither in hypophysectomized rats (STEINBERG et al. 1967) nor in immature rats (PLONNÉ et al. 1993), in which hepatic ER levels are low. Substitution of hypophysectomized rats with GH, which increases ER levels, in combination with ethinylestradiol results in hepatic LDL receptor levels almost as high as those in intact rats treated with ethinylestradiol alone (RUDLING et al. 1992).

As in the case with synthesis of coagulation factors and angiotensinogen in the liver, the effects of oral estrogens on blood lipids in humans by far surpass the effects of injected or percutaneous estrogens (MOORJANI et al. 1991). The 5- to 10-fold induction of LDL receptors in the rat with ethinylestradiol treatment cannot be equaled by the use of other hormones, including GH in the absence of estrogens (BRINDLEY and SALTER 1991). These data suggest at least a partially direct action of estrogens via the ER on hepatic LDL receptor levels.

The indirect actions of estrogens through alterations in secretion of GH and perhaps other hormones are possibly of equal importance. For example GH injections to healthy individuals increase hepatic LDL receptors and decrease plasma cholesterol levels (RUDLING et al. 1992), and GH-deficient patients have an increased mortality in myocardial infarction (ROSÉN and BENGTSSON 1990). While the stimulatory effects of estrogens on hepatic LDL receptors in the rat require pharmacological doses of ethinylestradiol, variations in blood lipids in humans occur during the menstrual cycle (SCHIJF et al. 1993). On the other hand, variations in GH secretion have been reported during the menstrual cycle (FARIA et al. 1992). Therefore, the observed changes in blood lipids might also be due to alterations in serum concentrations of GH secondary to cyclic estradiol variations. Postmenopausal estrogen treatment has been reported to increase GH secretion (DE LEO et al. 1993), but the relevance of this finding with respect to effects on blood lipids in unclear, since orally administered estrogens have a greater impact on the lipid profile than transdermal estrogens (MOORJANI et al. 1991).

There is a clear difference in morbidity and mortality rates in cardiovascular disease between males and females (GANGAR et al. 1993). This difference almost disappears at the onset of menopause, after which the female mortality in cardiovascular disease rises abruptly (WITTEMAN et al. 1989).

Postmenopausal estrogen therapy reduces the risk for myocardial infarction by approximately 50% (Sitruk-Ware and de Palacios 1989; Newnham 1993; Psaty et al. 1993). Initially, it was believed that most, if not all antiatherosclerotic effects of estrogens were mediated through the liver by induction of a "healthy" blood lipid profile (Brindly and Salter 1991). Estrogen treatment decreases cholesterol and increases triglyceride levels in serum (Basdevant 1992), but most importantly, induces a "healthy lipid profile" by decreasing the LDL/HDL ratio (Crosignany 1992). Decrease of serum LDL is accomplished by an increase in hepatic LDL receptor levels (Rudling 1987). Serum HDL levels are believed to be increased by an increase in apolipoprotein A synthesis (Moorjani et al. 1991) and a decrease in hepatic lipase activity (Tikkanen et al. 1982). The second mechanism may actually decrease cholesterol transport from peripheral tissues to the liver and is not necessarily salubrious (von Schoultz et al. 1989).

Estrogens are often given in combination with progestogens, which diminish the positive lipid profile, and it has not yet been clarified whether the addition of progestogens affects the risk of developing cardiovascular disease during estrogen treatment (Falkeborn et al. 1992; Psaty et al. 1993). The general belief, today, is that the positive lipid profile alone does not account for all effects of estrogens in cardiovascular disease, and that their effects on lipids may be of less importance than direct effects on blood vessels (L'Hermite 1990). Estrogens have vasodilatory effects on arteries (Magness and Rosenfeldt 1989; Mügge et al. 1993; Riedel et al. 1995), possibly mediated by stimulation of local prostacyclin or nitric oxide (NO) synthesis (Gangar et al. 1993). ERs have been detected in blood vessels (Campisi et al. 1993) and in vascular smooth muscle (Orimo et al. 1993). Another demonstrated effect of estrogens, possibly involved in slowing the artherosclerotic process, is inhibition of LDL oxidation (Rifici and Khachadurian 1992; Mooradian 1993).

Compared with the lipid effects of estrogens alone, a combined therapy with progestogens may induce atherosclerosis (Psaty et al. 1993). The addition of tamoxifen to estrogen-primed postmenopausal women induced significant effects on the lipoprotein pattern that should be considered as purely antiestrogenic (Ottosson 1984). HDL cholesterol and apolipoprotein A levels were significantly reduced after 3 months tamoxifen treatment (Ottosson 1984). Total and LDL cholesterol levels fell significantly in women treated with tamoxifen only, improving the lipid profile (Love et al. 1994; Grey et al. 1995; Mannucci et al. 1996). Raloxifene, in a 8-week study in postmenopausal women, decreased LDL cholesterol in the same range as conjugated estrogens, and serum cholesterol was also decreased (Draper et al. 1996).

D. Carbohydrates

Several other hormones, such as insulin, glucagon, corticoids, growth hormone and catecholamines, are more important than estrogen in carbohydrate

metabolism. The multitude of complex interactions makes it difficult to study the effect of estrogens only. Both "natural" and synthetic estrogens induce a decreased glucose tolerance and increased insulin levels. Data are contradictory, but the differences in effects are most likely dose dependent. The estrogens seem rather to have a transient reversible hyperglycemic rather than primarily diabetogenic effect (VAN KEEP et al. 1982). Diabetes is no absolute contraindication to estrogen treatment. The deterioration of carbohydrate tolerance that has been associated with oral contraceptives has been suggested to be caused mainly by the progestogen and not the estrogen (L'HERMITE 1990; GASPARD 1989). Hormone-replacement therapy with equine estrogens or estradiol valerate does not seem to induce impaired glucose tolerance (THOM et al. 1977; LARSSON-COHN and WALLENTIN 1977). It has even been suggested that the use of estrogen alone may improve glucose tolerance by enhancement of insulin receptor binding (SPELLACY et al. 1987). Improved glucose tolerance has been reported after 6 months of replacement therapy in women with reduced glucose tolerance (LUOTOLA et al. 1986).

An improvement of glucose tolerance following physiological estrogen treatment is also in agreement with the diminished insulin sensitivity, glucose intolerance and *acanthosis nigricans* found in a man with a disrupted ER and subsequent lack of estrogen responsiveness (SMITH et al. 1994). *Acanthosis nigricans* is a cutaneous marker of insulin resistance, especially when insulin resistance is associated with relative hyperandrogenism (BARBIERI and RYAN 1993). An increase in estrogens improves glucose tolerance by enhancing either target tissue responsiveness to insulin or insulin secretion (SHARP and DIAMOND 1993; LEITER et al. 1987; PROCHAZKA et al. 1986).

Insulin resistance associated with estrogen deficiency may in fact be reversed by physiological estrogen replacement. However, excessive estrogen action clearly deteriorates carbohydrate metabolism, possibly via increased glucocorticoid action. Also, progesterone and certain progestogens may induce insulin resistance and add to a pharmacological estrogenic effect (GODSLAND 1996).

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